



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

EMA/CHMP/166753/2023  
Committee for Medicinal Products for Human Use (CHMP)

## Assessment report

### **IDELVION**

International non-proprietary name: albutrepenonacog alfa

Procedure No. EMEA/H/C/003955/0000

### **Note**

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.



Status of this report and steps taken for the assessment				
Current step	Description	Planned date	Actual Date	Need for discussion
<input type="checkbox"/>	Start of procedure	13 Apr 2022	13 Apr 2022	<input type="checkbox"/>
<input type="checkbox"/>	CHMP /PRAC Rapporteurs Joint Assessment Report	16 May 2022	17 May 2022	<input type="checkbox"/>
<input type="checkbox"/>	PRAC Rapporteur Assessment Report	23 May 2022	N/A	<input type="checkbox"/>
<input type="checkbox"/>	PRAC members comments	25 May 2022	25 May 2022	<input type="checkbox"/>
<input type="checkbox"/>	CHMP members comments	30 May 2022	30 May 2022	<input type="checkbox"/>
<input type="checkbox"/>	Updated PRAC Rapporteur Assessment Report	31 May 2022	31 May 2022	<input type="checkbox"/>
<input type="checkbox"/>	Updated CHMP/PRAC Rapporteurs Joint Assessment Report	02 Jun 2022	02 Jun 2022	<input type="checkbox"/>
<input type="checkbox"/>	PRAC endorsed relevant sections of the assessment report <sup>3</sup>	08 Jun 2022	08 Jun 2022	<input type="checkbox"/>
<input type="checkbox"/>	Start of written procedure	08 Jun 2022	08 Jun 2022	<input type="checkbox"/>
<input type="checkbox"/>	Request for Supplementary Information	10 Jun 2022	10 Jun 2022	<input type="checkbox"/>
<input type="checkbox"/>	Restart date	30 Aug 2022	30 Aug 2022	<input type="checkbox"/>
<input type="checkbox"/>	CHMP/PRAC Rapporteurs 1st Response Assessment Report	10 Oct 2022	10 Oct 2022	<input type="checkbox"/>
<input type="checkbox"/>	PRAC members comments	14 Oct 2022	14 Oct 2022	<input type="checkbox"/>
<input type="checkbox"/>	CHMP comments	17 Oct 2022	17 Oct 2022	<input type="checkbox"/>
<input type="checkbox"/>	Updated CHMP/PRAC Rapporteurs Assessment Report	18 Oct 2022	18 Oct 2022	<input type="checkbox"/>
<input type="checkbox"/>	PRAC outcome	25 Oct 2022	25 Oct 2022	<input type="checkbox"/>
<input type="checkbox"/>	Start of written procedure	25 Oct 2022	25 Oct 2022	<input type="checkbox"/>
<input type="checkbox"/>	Request for Supplementary Information	27 Oct 2022	27 Oct 2022	<input type="checkbox"/>
<input type="checkbox"/>	Restart date	15 Dec 2022		<input type="checkbox"/>
<input type="checkbox"/>	CHMP/PRAC Rapporteurs' 2 <sup>nd</sup> Joint Response Assessment Report	03 Jan 2023	03 Jan 2023	<input type="checkbox"/>
<input type="checkbox"/>	Updated CHMP/PRAC Rapporteurs' 2 <sup>nd</sup> response Assessment Report	09 Jan 2023	09 Jan 2023	<input type="checkbox"/>
<input type="checkbox"/>	Responses to 3d RSI	24 Jan 2023	24 Jan 2023	<input type="checkbox"/>
<input type="checkbox"/>	CHMP/PRAC Rapporteurs' 3 <sup>rd</sup> Joint Response Assessment Report	08 Feb 2023	08 Feb 2023	<input type="checkbox"/>
<input type="checkbox"/>	CHMP/PRAC comments	13 Feb 2023	13 Feb 2023	<input type="checkbox"/>
<input type="checkbox"/>	Updated CHMP/PRAC Rapporteurs' 3 <sup>rd</sup> Joint Response Assessment Report	16 Feb 2023	N/A	<input type="checkbox"/>
<input checked="" type="checkbox"/>	Opinion	23 Feb 2023	23 Feb 2023	<input type="checkbox"/>

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# 1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, CSL Behring GmbH submitted to the European Medicines Agency on 7 April 2022 an application for a variation.

The following changes were proposed:

Variation requested		Type	Annexes affected
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I and IIIB

Update of sections 4.2, 4.8 and 5.1 of the SmPC in order to update information and amend the frequencies of adverse drug reactions (ADRs) based on the final results from study CSL654\_3003 listed as a category 3 study in the RMP; this is an open-label, multicentre, uncontrolled study to evaluate the safety, pharmacokinetics and clinical response of rIX-FP with regard to the prevention and treatment of bleeding in previously untreated patients (PUPs) with Haemophilia B. The Package Leaflet is updated accordingly.

The RMP version 4.1 has also been submitted (response to 2<sup>nd</sup> RSI).

In addition, the MAH took the opportunity to introduce minor editorial changes to the PI and update the list of local representatives in the Package Leaflet.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

This application relates to paediatric studies submitted according to Article 46 of the paediatric Regulation.

## 2. Overall conclusion and impact on the benefit/risk balance

Arm 4 of study CSL654\_3003 was conducted to obtain safety and efficacy information for the use of rIX-FP in PUPs with severe hemophilia B and to collect information on inhibitor formation in PUPs 0 to < 18 years of age. The study was prematurely stopped, and 12 PUPs were actually treated with rIX-FP.

Pharmacokinetic evaluation comprises 8 data-sets with 3 sampling time-points for obtaining Incremental Recovery (IR) and  $c_{max}$ . Residual FIX-levels of previous treatments impair the value of the results. In the age-group 0-6 years ( $n=7$ ), median IR was 1.2 ([IU/dL]/[IU/kg]),  $c_{max}$  was about 63 IU/dL, and trough levels after 7 days were 11.85 IU/dL with wide ranges. Lower bound of trough levels was 2.7 IU/dL.

The only patient within the older paediatric age group (11 years) had significantly lower IR and  $c_{max}$  values, and did not reach measurable steady-state results (below level of quantification). This patient developed high-titre inhibitor with hypersensitivity.

Efficacy evaluation was based upon Annualized Bleeding Rates (ABRs), consumption of FIX, and treatment response. Presentation of respective results require further amendments.

One subject entered the surgery sub-study for port insertion. Two additional subjects underwent surgical procedures.

Adverse Event profile in general seems to be in accordance with the age-group. A high number of 9 hypersensitivities, 4 rashes and 2 urticarias in this narrow patient group were subject to further discussion. One 11 year old subject suffered from high-titre inhibitor with hypersensitivity.

Overall, results of the study have been amended according to the clinical guideline. Product information and Clinical Overview have been amended, accordingly.

The updated RMP version 4.1 can be considered acceptable (see section 15).

The benefit-risk balance of IDELVION remains positive.

### 3. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation requested		Type	Annexes affected
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I and IIIB

Update of sections 4.2, 4.8 and 5.1 of the SmPC in order to update information and amend the frequencies of adverse drug reactions (ADRs) based on the final results from study CSL654\_3003 listed as a category 3 study in the RMP; this is an open-label, multicentre, uncontrolled study to evaluate the safety, pharmacokinetics and clinical response of rIX-FP with regard to the prevention and treatment of bleeding in previously untreated patients (PUPs) with Haemophilia B.

The Package Leaflet is updated accordingly.

The RMP version 4.1 has also been submitted (response to 2<sup>nd</sup> RSI) and can be accepted.

In addition, the MAH took the opportunity to introduce minor editorial changes to the PI and update the list of local representatives in the Package Leaflet.

In addition, this application relates to paediatric studies submitted according to Article 46 of the paediatric Regulation.

☒ is recommended for approval.

#### ***Amendments to the marketing authorisation***

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.

## 4. EPAR changes

**Rapporteur's comment:** EPAR amendment should follow the scope of Article 46, Paediatric Regulation.

The table in Module 8b of the EPAR will be updated as follows:

### ***Scope***

Please refer to the Recommendations section above

### ***Summary***

Please refer to Scientific Discussion 'Idelvion-H-C-3955-II-59'

Submission of the final results from study CSL654\_3003 which is an open-label, multicentre, uncontrolled study to evaluate the safety, pharmacokinetics and clinical response of rIX-FP with regard to the prevention and treatment of bleeding in previously untreated patients (PUPs) with Haemophilia B (listed as category 3 RMP study). Consequently, sections 4.2, 4.8 and 5.1 of the SmPC have been updated to update the information and amend the frequencies of adverse drug reactions (ADRs).

For more information, please refer to the Summary of Product Characteristics.



## **Annex: Rapporteur's assessment comments on the type II variation**

### **5. Introduction**

#### Regulatory aspects:

The MAH submitted the Clinical Study Report of *CSL654\_3003 PUP* with respective SmPC and RMP updates.

With the submission of this variation, the MAH considers that the required additional pharmacovigilance activity *CSL654\_3003* Clinical study (category 3 study in Table Part III.3-1) has been completed and requests this MEA to be considered fulfilled.

With the completion of *CSL654-3003 – PUP CSR*, the MAH has finalized all studies agreed in the paediatric investigation plan 001107-PIP01-10-M04. A compliance check has been performed.

Publication of the outcome of the current procedure should follow Article 46 of the Paediatric Regulation.

#### Clinical aspects:

Study *CSL654\_3003* was conducted to obtain safety and efficacy information for the use of rIX-FP in PTPs and PUPs (Arm 4) with severe hemophilia B and to collect information on inhibitor formation in PUPs 0 to < 18 years of age. At least 20 PUPs were planned to be enrolled in the study initially, in line with the respective Clinical Guideline [2011]. After the PUP study started, the guideline was updated, and PUP studies were no longer required [2018]. Subsequently, the MAH stopped enrollment in accordance with the PDCO (EMA-001107-PIP01-10-M04). 12 PUPs were actually treated with rIX-FP.

Study 3003 was completed (last patient visit) in June 2021 for PUPs (Arm 4).

### **6. Clinical Pharmacology aspects**

FIX activity after a single dose of 50 international units (IU)/kg rIX-FP was analyzed using non-compartmental pharmacokinetic (PK) analysis. Maximum concentration (C<sub>max</sub>) and incremental recovery (IR) were presented. Because of considerable residual levels of previous product evident at predose (eg, due to prior rIX-FP dosing), calculations of baseline-corrected PK parameters (by subtraction of the predose FIX activity level from subsequent postdose levels) were limited to IR and maximum concentration (C<sub>max</sub>). In addition, observed trough and steady-state FIX activity during the efficacy period were recorded.

#### **6.1. Methods – analysis of data submitted (CSR and Clinical Overview)**

PK assessment of 50 IU/kg rIX-FP with selected time points, or IR, was in general done at the beginning of the study. Blood sampling for measurement of plasma FIX activity (central laboratory) was done before infusion of rIX-FP, at 30 ± 5 minutes, at 72 ± 24 hours (ie, 3 ± 1 day), and at 168 ± 24 hours (ie, 7 ± 1 days). Eight PUPs had sufficient FIX activity measurements to allow for non-compartmental estimation of IR and C<sub>max</sub>.

## 6.2. Results (CSR and Clinical Overview)

Median Incremental Recovery (IR) was 1.2 (IU/dL)/(IU/kg) with a range of 0.9 to 1.9 for 7 children <6yrs and 0.8 for one child of 11 years. Median baseline-corrected Cmax was 62.6 IU/dL for 7 children < 6yrs with a range of 45.2 to 83.8 and 39.9 mIU/dL for 1 child of 11 yrs:

**Table 1 Baseline-corrected FIX Activity PK Parameters Following Administration of rIX-FP by Dose (PUP PK Population)**

	Age: <6 yrs (N=7)	Age: ≥6 to ≤12 yrs (N=1)	Total (N=8)
Dose: 50 IU/kg			
<b>Incremental Recovery</b> ([IU/dL]/[IU/kg])			
n	7	1	8
Median	1.235	0.799	1.144
Min, Max	0.90, 1.86	0.80, 0.80	0.80, 1.86
<b>Max Conc</b> (Cmax) (IU/dL)			
n	7	1	8
Median	62.60	39.90	57.60
Min, Max	45.2, 83.8	39.9, 39.9	39.9, 83.8

Conc=Concentration, NC = Not Calculated, CV = Coefficient of Variation. data as of 29Jun2021.

Source: Listing 16.2.5.6.1.1.99, **From Table 14.2.7.2.2.99, CSR**

In those PUPs with available trough and steady-state values (N = 7), the median (range) observed trough and steady-state FIX activity was 11.85 with a range of 2.7 to 31.3 IU/dL:

**Table 2 Observed Trough and Steady-state FIX Activity on 7-day Prophylaxis Regimen (PUP Safety Population, Arm 4)**

	Age < 6 years N = 7	≥ 6 to ≤ 12 years N = 0 a	Total N = 7
<u>Observed trough FIX activity, IU/dL</u>			
Number of PK measurements	27	0	27
Median (min, max)	11.85 (2.7, 31.3)	-	11.85 (2.7, 31.3)
<u>Steady-state FIX activity, IU/dL</u>			
Number of PK measurements	19	0	19
Median (min, max)	11.85 (2.7, 31.3)	-	11.85 (2.7, 31.3)

FIX = coagulation factor IX; IU = international unit; max = maximum; min = minimum; N = total number of PUPs on regimen; PK = pharmacokinetic; PUP = previously untreated patient.

Note: Table includes observed trough and steady-state FIX PK samples only.

a The 11-year-old PUP had 1 trough value that was below the lower limit of quantification.

Source: CSR Tables 14.2.8.1.1.99 (trough) and 14.2.8.2.1.99 (steady-state); From Table 11-8, CSR

Trough FIX activity levels were defined as a subset of the collected FIX activity samples that were collected at a scheduled visit, measured at the central lab, but were not part of a PK collection or surgery sub-studies.

Steady-state FIX activity levels were defined as a subset of the trough FIX activity levels that were collected before a 3rd consecutive dose in the 14- or 10-day / 3 x per month prophylaxis regimens, or before a 4th consecutive dose on the 7-day prophylaxis regimen.

### **6.3. Discussion (Rapporteur)**

Database of 8 data-sets with only 3 sampling time-points for PK-data is considered to be narrow, and residual FIX-levels of previous treatments impair the value of the results. Median and range have been extracted by the Rapporteur as presented above. These are considered to be more adequate than mean-values for clinical purposes in such narrow data-base. The Clinical Overview Addendum should be updated, accordingly (Q).

PK-results:

Age-group 0-6 years (n=7): Incremental Recovery of 1.2 ([IU/dL]/[IU/kg]), C<sub>max</sub> of about 63 IU/dL, and trough levels after 7 days of 11.85 IU/dL are noted. The documented wide ranges are not unusual for the age-group. Of note, the lower bound of trough levels is 2.7 IU/dL, which is considered to be low but “protective” in the common understanding of activity levels.

Age group >6 years (n=1: 11 years): The only patient within the older paediatric age group (11 years) had untypical significantly lower IR and C<sub>max</sub> values, and did not reach measurable steady-state results (below level of quantification). These conflicting results have not been further commented. Further, table 11-8 of the CSR is misleading, as the “Total” column contains data of the lower paediatric age group, only. For interpretation of these results with respect to the 11 y/o subject, clinical/timely context of the PK- and trough-level-evaluations should be analysed with his inhibitor- with hypersensitivity-development (Q).

The number of patients with true severe Haemophilia B (<1% FIX activity) and – if appropriate, subgroup PK-analysis of only these data-sets should be amended for further discussion and reflection in the clinical Overview. (Q)

## **7. Clinical Efficacy aspects**

### **7.1. Methods – analysis of data submitted (CSR and Clinical Overview)**

Demography:

14 male PUPs were enrolled in Arm 4, and 12 PUPs were treated with rIX-FP with at least 1 dose. At the time of enrolment, most PUPs (N = 11) were < 6 years of age, with a mean (range) age of 0.4 (0 to 1) years. The only PUP ≥ 6 years of age was 11 years old and the only patient of Asian ethnicity. Ten PUPs (71.4%) completed the study who did not receive rIX-FP during the study. Four PUPs (28.6%) discontinued from the study for the following reasons:

2 due to withdrawal by subject

1 before receiving study treatment

1 due to the development of a high-titer FIX inhibitor:

## Subject Disposition Flowchart (PUPs, Arm 4)

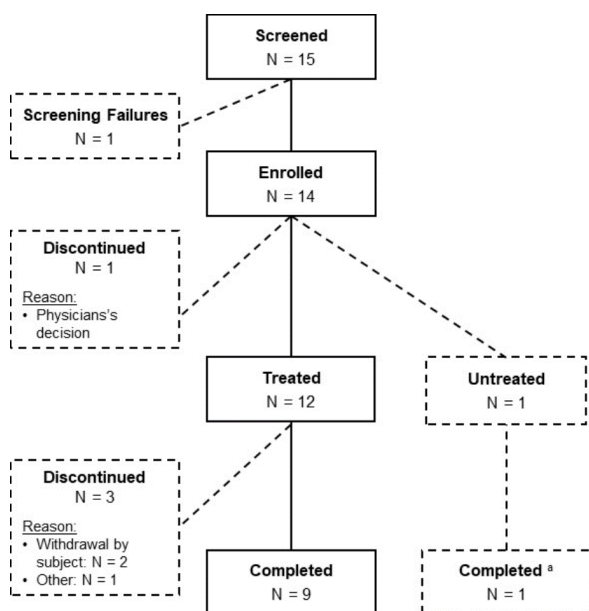


Figure 10-1 CSR

### Treatment:

5 subjects had an on-demand treatment period with rIX-FP before routine prophylaxis, and 7 subjects had routine prophylaxis immediately without a prior on-demand period. All 12 subjects received rIX-FP as routine prophylaxis on a 7-day regimen (N = 11) or 10-day regimen (N = 1). Following the development of an FIX inhibitor in 1 PUP, he was treated on an intensified treatment with rIX-FP.

Dosage for on-demand treatment was 35-75 IU/kg, Prophylaxis dose was 25-50 IU/kg for the 7-days scheme.

## 7.2. Results (CSR and Clinical Overview)

### Annualized Bleeding Rates:

#### Time on Study, by Study Period (PUP Safety Population, Arm 4)

	On demandProphylaxis Regimen				Intensified ment	Treat-Total
Parameter	N=6	7-Day N=11	10-Day N=1	Total N=12	N=1	N=12
Time on period, months						
Median	10.79	10.87	12.12	11.50	20.24	22.65
(min, max)	1.9, 12.3	(3.1, 32.3)	(NA)	(3.1, 32.3)	(NA)	(4.5, 33.0)
Time on period, weeks						
Median	46.93	47.29	52.71	50.00	88.0	98.50
(min, max)	(8.3, 53.6)	(13.4, 140.3)	(NA)	(13.4, 140.3)	(NA)	(19.6, 143.4)

max = maximum; min = minimum; NA = not applicable; PUP = previously untreated patient. Note: Analysis excludes the exposure in the PK and surgery periods.

One subject developed inhibitor to FIX

Source Table 14.1.4.2.1.99, Table 10-3 CSR

In the 11 PUPs of Study 3003 on the 7-day prophylaxis regimen, total annualized bleeding rate (ABR) ranged from 0 to 3.89. Five of the 11 PUPs had an ABR of 0 and 8 PUPs had an annualized spontaneous bleeding rate (AsBR) of 0.

23 joint bleeding episodes were reported in 6 PUPs: 13 episodes were reported in the 11-year-old subject with target joints while on intensified treatment after inhibitor development; 4 joint bleeding episodes were reported in 1 PUP during 7-day prophylaxis; for the remaining 4 PUPs,  $\leq 2$  joint bleeding episodes were reported.

### Treatment response:

No major bleeding episodes were reported in any PUP during the study. There were a total of 44 non-major bleeding episodes in the 12 PUPs in Study 3003. Of those, 37 bleeding episodes were treated with rIX-FP. Of the 37 treated bleeding episodes, 16 were spontaneous, 17 traumatic, and 4 of unknown cause. Across the prophylaxis, on demand, and intensified treatment periods. 93.8% of spontaneous bleeding events were successfully controlled with 1 or 2 rIX-FP infusions.

## Consumption:

**Table 11-6 Consumption of rIX-FP by Study Period (PUP Efficacy Population, Arm 4)**

Parameter	On-demand Period N = 6	Prophylaxis Regimen			Intensified Treatment N = 1	Total N = 12
		7-day N = 11	10-day N = 1	Total N = 12		
Number of PUPs on treatment	5	11	1	12	1	12
Total number of rIX-FP infusions	11	720	32	752	26	789
Mean dose (IU/kg)						
Mean (SD)	60.26 (25.313)	45.49 (4.491)	50.00 (NA)	45.87 (4.475)	92.00 (NA)	52.43 (17.443)
Median (min, max)	63.70 (34.0, 97.1)	47.80 (36.4, 50.1)	50.00 (NA)	47.80 (36.4, 50.1)	92.00 (NA)	47.90 (34.0, 97.1)
Total dose per infusion (IU/kg)						
Mean (SD)	60.56 (24.477)	46.24 (7.938)	50.03 (0.343)	46.40 (7.805)	92.02 (24.593)	48.10 (12.386)
Median (min, max)	50.00 (30.8, 102.0)	47.70 (28.1, 98.4)	50.00 (49.2, 51.5)	48.15 (28.1, 98.4)	99.90 (8.2, 101.3)	48.20 (8.2, 102.0)
Number of infusions per month						
Mean (SD)	0.30 (0.141)	4.27 (0.350)	2.60 (NA)	4.13 (0.587)	1.30 (NA)	2.91 (1.855)
Median (min, max)	0.30 (0.1, 0.5)	4.40 (3.5, 4.7)	2.60 (NA)	4.35 (2.6, 4.7)	1.30 (NA)	3.95 (0.1, 4.7)
Monthly dose (IU/kg)						
Mean (SD)	16.10 (5.331)	193.66 (17.066)	132.10 (NA)	188.53 (24.096)	118.2 (NA)	136.73 (81.097)
Median (min, max)	17.80 (8.2, 20.7)	194.70 (169.7, 215.6)	132.10 (NA)	191.90 (132.1, 215.6)	118.2 (NA)	173.55 (8.2, 215.6)

IU = international unit; max = maximum; min = minimum; PUP = previously untreated patient; NA = not applicable; rIX-FP = recombinant fusion protein linking coagulation factor IX with albumin.

Source: [Table 14.2.5.1.2.99](#)

## Surgery

One PUP entered the surgery substudy. Limited PK and efficacy data were collected for this PUP. An additional 2 PUPs underwent a total of 3 surgical procedures, but were not enrolled into the surgery substudy (which was optional). No PK or efficacy data were reported for these PUPs during surgery.

### **7.3. Discussion (Rapporteur)**

One 11-year-old subject (age group 6-12 years) was included. In patients with severe haemophilia it is not plausible that no factor-replacement has been administered up to this age. Clinical details beyond the provided case-narrative regarding history, and haemophilia-type and -severity of this patient should be amended for better understanding. (Q) Of note, this patient developed high-titre inhibitor with hypersensitivity, and was the only patient with Asian ethnicity.

Annualized Bleeding Rates (ABRs): Treatment periods of at least 6 months are requested for calculating ABRs in subjects on prophylaxis due to individual and seasonal confounding factors. Further, only total ABR is of relevance as "spontaneous" bleed is no standardized term. Total ABRs for all subjects beyond 6 months of prophylaxis, and individual ABR together with individual treatment duration might give further insight in bleeding pattern of the individual patients. (Q)

Consumption: Consumption is understood as an efficacy parameter and should be presented in line with the current clinical guideline (EMA/CHMP/BPWP/144552/2009 rev. 2 Corr). For prophylaxis, dose per kg per month and year for patients on prophylaxis >6 months, and for on-demand treatment the dose per kg per event (bleeding episode) - and not per infusion - should be available. For on-demand treatments, the dose per kg per bleeding event should be available at least for all bleeds (total), spontaneous, and traumatic bleeds. Data should be presented as median and range. (Q)

Treatment response: Treatment success for 16 spontaneous bleeds was 93.8% with 1 or 2 doses. According to the Clinical Guideline, treatment response should be presented as "none", "moderate", "good" or "excellent". Response of all 37 bleeding episodes (spontaneous, traumatic, and of unknown cause) should be amended. (Q)

Surgery: One subject entered the surgery substudy for port insertion for a "surgery period" of 8 days. Total consumption per kg and surgical procedure should be available.

2 additional subjects underwent surgical procedures: 1 underwent (1) port insertion and (2) bilateral ear-tube-insertion. 1 patient underwent revision of sagittal suture cranio-synostosis. The latter surgery is considered major. Available data on total consumption for all surgeries should be provided as far as available. (Q)

Overall, the presented efficacy data seem to correspond with similar replacement products. Some data should be amended according to the clinical guideline. The Overview should reflect respective key data, and relevant results of interest for Idelvion. Due to the narrow data base and the short treatment intervals (EDs), summary-numbers might not be representative for the whole PUP-population.

Surgery-data are expected to be amended.

## 8. Clinical Safety aspects

### 8.1. Methods – analysis of data submitted (CSR and Clinical Overview)

Safety was assessed in all PUPs of Study 3003 who received  $\geq 1$  infusion of rIX-FP as part of either PK evaluation, on-demand treatment, routine prophylaxis, or perioperative management. Safety assessments included adverse events (AEs), biochemistry, hematology, local tolerability, vital signs, and physical examinations. Important identified risks associated with rIX-FP therapy include Hypersensitivity / Anaphylactic Reactions and the Development of Inhibitors to FIX. Important potential risks include Thromboembolic Events and the Development of Antibodies Against Chinese Hamster Ovary (CHO) Host Cell Proteins.

Safety Population included 5 subjects in Europe, 4 subjects in North America, and 3 subjects in Oceania. Primary safety endpoint was the development of inhibitors against FIX. Secondary safety endpoint was the occurrence of AEs and related AEs to rIX-FP.

Adverse events of special interest (AESIs) included PTs associated with the following Standardized MedDRA Queries (SMQs) narrow search terms: 1) Anaphylactic Reactions, 2) Hypersensitivity, and 3) Embolic and Thrombotic events.

### 8.2. Results (CSR and Clinical Overview)

#### Exposure:

#### Exposure Days (excluding PK and surgery)

Parameter	On-demand period N=6	Prophylaxis Regimen			Intensified N=1	Total N=12
		7-day N=11	10-day N=1	Total N=12		
EDs						
Mean (SD)	2.2 (1.30)	65.5 (42.06)	32.0	62.7 (41.25)	26.0	65.8 (38.69)
Median	2	49.0	32.0	47.0	26.0	49.0
(min, max)	(1, 4)	(12, 145)	(NA)	(12, 145)	(NA)	(21, 145)
Number of PUPs (n [%]) with						
< 50 EDs	5 (83.3)	6 (54.5)	1 (100.0)	7 (58.3)	1 (100.0)	7 (58.3)
≥ 50 to <75 EDs	0	1 (9.1)	0	1 (8.3)	0	1 (8.3)
≥ 75 to < 100 EDs	0	1 (9.1)	0	1 (8.3)	0	1 (8.3)
≥ 100 EDs	0	3 (27.3)	0	3 (25.0)	0	3 (25.0)

ED = exposure day; max = maximum; min = minimum; NA = not applicable; PUP = previously untreated patient; rIX-FP = recombinant fusion protein linking coagulation factor IX with albumin.

Notes: An ED was defined as any day that the PUP received an rIX-FP infusion, regardless of the number of infusions on that day.

Percentages were based on the number of PUPs in the Safety Population in each respective study period. PUPs who participated in multiple periods were counted in each period in which they participated.

Analysis excludes exposure in the PK and surgery periods.

One PUP did not receive rIX-FP during the on-demand period; therefore, analysis of EDs was performed for 5 PUPs in the on-demand period.

Source: Table 14.1.4.2.1.99, Table 12-1 CSR

Overall, 7 of 12 subjects had less than 50, 1 subject between 75 to 100, and 3 subjects above 100 EDs.



### Adverse Events:

Summary: During the on-demand period, 5 of 6 subjects experienced a total of 17 TEAEs. No TEAEs were reported during the PK period. During prophylaxis, 11 of 12 subjects experienced a total of 109 TEAEs. One 11-year-old experienced a TEAE of hypersensitivity leading to withdrawal of rIX-FP (see below).

5 PUPs (41.7%) had 5 SAEs (Influenza, Device Related Infection, Head Injury, Pneumonia, and Anti Factor IX Antibody Increased. Of these, 1 SAE of Anti Factor IX Antibody Increased was assessed as related to rIX-FP by the Investigator and was also considered an AESI.

3 PUPs had 9 AESIs. All of the AESIs were hypersensitivities (including Rash and Urticaria). Four of these were assessed to be related: 1 event of Rash in a PUP < 6 years of age and 3 events of Hypersensitivity in the 11-year-old PUP who developed the FIX inhibitor. There were no AESIs of anaphylaxis or thromboembolic events.

Inhibitor development: No subject < 6 years developed an inhibitor to FIX. The only subject > 6 years, an 11-year-old male, experienced inhibitor development with hypersensitivity reactions and was discontinued from the study.

The respective narrative reads (abbreviated) as follows:

The child did not test positive for inhibitors to FIX or antibodies to CHO cell proteins. On 17 June 2015 after 8 EDs of rIX-FP, the subject developed a low-titer inhibitor to FIX. On 10 July 2015, the subject experienced a mild TEAE of Hypersensitivity during the routine prophylaxis IX-FP infusion, and the infusion was interrupted. On 31 July 2015, the inhibitor titer was measured to be 5.61 BU/mL (high-titer inhibitor). The subject received a dose of 100 IU/kg rIX-FP on the same day. From March 2016, the subject received a once-weekly intensified treatment regimen (100 IU/kg) over approximately the next 2 months but continued to experience bleeding events in the knee joint. On 11 May 2016, the inhibitor titer was 26.1 IU/kg. From 16 May 2016, intensified treatment was switched from once weekly to on-demand, and the inhibitor titer began to decrease. The subject further experienced bleeding events, was administered rIX-FP, and experienced 2 related events of Hypersensitivity – one described with symptoms of pallor, fever, respiratory rate increased, and abdominal pain - leading to discontinuation from the study drug. At the time of study discontinuation, the inhibitor titer of the PUP was 66 BU/mL, and the SAE of Anti Factor IX Antibody Increased was not considered resolved.

### Postmarketing experience:

Overall, the reporting rate for inhibitor development from the postmarketing population remains to be low.

Up to the Data Lock Point, there have been 5 case reports of inhibitor development to rIX-FP captured in the global safety database, which includes evidence of a positive inhibitor test. The case report of inhibitor development in the child PUP in Study 3003 has also been captured in the global safety database. Of the cumulative 6 reports, 5 cases of inhibitor development were in the pediatric population, and 1 was in an adult.

### **8.3. Discussion (Rapporteur)**

Exposure: Relevant core parameter with respect to the primary clinical endpoint (development of inhibitors against FIX) is the number of Exposure Days (mainly above and below 50 EDs): Seven out of 12 subjects had less than 50 EDs. One of those developed an inhibitor after 8 EDs. Five subjects were treated for  $\geq 50$  EDs.

Adverse Event profile in general seems to be in accordance with the age-group.

The presentation of clinically relevant events is not considered to be meaningful. At least, the hypersensitivity reactions based on the MedDRA SMQ should be clearly described: 9 “hypersensitivity reactions” in this narrow patient group have been described in section 12.3.1 of the CSR; Table 12-3 in the CSR displays 2 events of urticaria, and 4 events of rash; Table 12-4 presents 3 “hypersensitivities” within 72 hours; Table 12-6 (SMQ search) presents 9 “hypersensitivities”, 4 “rashes”, and 2 “urticarias”. This divergent information is considered to be not meaningful for assessing this clinically relevant entity of hypersensitivity-reactions (Q).

Inhibitor development: One out of 12 subjects suffered high-titer inhibitor development with hypersensitivity. However, 7 of these subjects had less than 50 EDs. Consequently, there was one in 6 subjects, suffering inhibitor development or reaching  $\geq 50$ EDs. This has to be seen in correlation with a rare inhibitor incidence in Hemophilia B, in general (1.5-3%). Further, the presentation of the “hypersensitivities” in this only inhibitor patient to be “mild” (section 12.4.3.3, CSR) is misleading – as generalized symptoms with stop of infusion were described, and the last event was reason for withdrawal from the study.

Device related complications: Such events are considered to be “expected events” per definition. However, these should be analysed and presented as “significant” AEs in the respective section (CSR 12.4.2), adequately. At least one subject experienced an SAE of “Device Related Infection” (Q).

Post-marketing experience on inhibitor development is – with the exception of 1 report in the PUP-population of study 3003 – not in the scope of this assessment. The number of 6 cumulative inhibitor-reports is noted.

## 9. Risk management plan

### 9.1. Safety Specification

#### *Epidemiology of the indications and target population*

**PRAC Rapporteur assessor's comment:**

The section on prevalence of Hemophilia B was updated. Several administrative updates were performed on demographics. Treatment options, natural history and age-related comorbidities were described. All amendments can be considered acceptable.

#### *Clinical trial exposure*

Study CSL654\_3003 was completed. This study was a Study 3003 was a phase 3b open-label, multicenter, safety, and efficacy extension study of rIX-FP in subjects with hemophilia B. In total, 12 PUPs completed the study.

**PRAC Rapporteur assessor's comment:**

The clinical trial exposure was updated with information on study 3003, including addition of exposure in PUPs by regimen (table SIII-2). The cumulative clinical trial exposure rIX-FP for all studies added in tables by EDs is presented in Table SIII-3a and b, by age in Table SIII-4, by dose in Table SIII-5a and 5b, and by ethnic origin in Table SIII-6, respectively. Overall, 126 (only male) patients were treated with rIX-FP.

The changes in this section of the RMP are acceptable.

#### *Populations not studied in clinical trials*

**PRAC Rapporteur assessor's comment:**

Table SIV.3 1: Exposure of special populations included or not in clinical trial development programs now includes information on study 3003. Accepted.

#### *Post-authorisation experience*

**PRAC Rapporteur assessor's comment:**

The method to calculate exposure was removed. The cumulative exposure table was updated with sales volumes. Accepted.

## Identified and potential risks

Summary of the safety concerns

**RMP v4.0**

Summary of safety concerns	
Important identified risks	<ul style="list-style-type: none"><li>Hypersensitivity / anaphylactic reactions</li><li>Development of inhibitors to factor IX</li></ul>
Important potential risks	<ul style="list-style-type: none"><li>TEEs</li><li>Development of antibodies against CHO host cell proteins</li><li>Dosing errors based on variability in the assays used during treatment monitoring of factor IX levels</li></ul>
Missing information	<ul style="list-style-type: none"><li>Experience in patients with severe renal or hepatic impairment</li><li>Efficacy and safety in PUPs</li><li>Experience in pregnancy and lactation, including labor and delivery</li><li>Experience in elderly patients (aged 65 years and above)</li><li>Experience in patients for ITI (off-label use)</li></ul>
CHO, Chinese hamster ovary; ITI, immune tolerance induction; PUPs, previously untreated patients; rIX-FP, recombinant fusion protein linking coagulation factor IX with albumin; TEEs, thromboembolic events	

The MAH provided rationale on removal of important potential risks and all of the missing information from the list of safety concerns.

### **Important potential risks:**

- **Development of Antibodies against CHO Host Cell Proteins-**

#### Historical reason/ perspective for inclusion:

Host cell proteins are a complex and heterogeneous group of impurities with substantial differences in isoelectric point, structure, molecular mass, and hydrophobicity properties. This makes the identification and elimination of these proteins difficult [Bailey- Kellogg et al, 2014].

These process impurities are a known risk for biological products in general. Although the severity and nature of this risk are currently unknown, the CHO genome contains many proteins that are substantially dissimilar to the human genome from the T cell epitope standpoint, and thus inherently pose some risk of triggering anti-self-immune response [Bailey-Kellogg et al, 2014]. Patients with a known allergy to hamster protein are particularly at risk.

#### Reason for proposed removal:

There are no estimates for development of antibodies to CHO host cell proteins to recombinant FIX products or any of its excipients, including hamster cell protein in the published literature to date. There are no reports of antibody development to CHO host cell proteins received from clinical studies on rIX-FP, and there are no reports from post- marketing experience to date.

This risk of triggering an immune response is already monitored under the medical concept of hypersensitivity anaphylactic reactions and development of inhibitors to factor IX (important identified risks). Additionally, information on allergy to hamster protein in the product labeling (under contraindications and special warnings and precautions) and routine monitoring of post-marketing data for hypersensitivity/ anaphylactic reactions and inhibitor development to FIX are considered sufficient.

**PRAC Rapporteur assessor's comment:**

Neither in clinical studies including the study assessed in this procedure (study 3003) nor in the PSURs, cases of antibodies to CHO host cell proteins have been reported. It is agreed with the MAH that immune responses are monitored as well under the identified risks of Hypersensitivity/anaphylactic reactions and Development of inhibitors to FIX. The labelling includes a contraindication in section 4.3 (allergy to hamster protein), warning under hypersensitivity in section 4.4 and description of rare development of antibodies to hamster protein with related hypersensitivity reactions under section 4.8 of the PI. The risk is considered covered in the labelling and is accepted for removal.

- **Dosing Errors based on variability in assays used during treatment monitoring of factor IX levels**

**Historical reason/ perspective for inclusion:**

One-stage clotting assay (OSC) is a routinely used assay for potency labeling of factor concentrate vials as well as for clinical monitoring of patients. Substantial inter-laboratory variability has been reported for OSCs when measuring the activity of factor replacement products due to the wide range of currently available activated partial thromboplastin time reagents, calibration standards, factor-deficient plasmas, assay conditions and instruments, and lack of international standardization for OSC assays has been noted across FIX products in general [Marlar et al, 2020].

These discrepancies between measurements could potentially expose the patients to under-/overdosing.

**Reason for proposed removal:**

There are no reports of medication errors indicating underdosing and overdosing due to assay issues and no reports of associated AEs due to assay issues for rIX-FP from post-marketing experience to date. There are no safety findings linked to dosing errors based on variability in assays reported for rIX-FP in the published literature [Ovanesov et al, 2020]. Furthermore, the impact of dosing errors on the individual patient due to variability in assays can be considered as low with most specialist coagulation laboratories being aware of this situation in general [Ovanesov et al, 2020].

The information provided on treatment monitoring with OSCs in the product labeling, together with awareness of this issue amongst specialist coagulation laboratories in the marketplace and continued routine monitoring of medication errors are considered sufficient.

**PRAC Rapporteur assessor's comment:**

In the last PSUR procedure (EMA/H/C/PSUSA/00010497/202101) 5 initial cases of medication error were reported (2 cases associated with adverse event, 3 cases without adverse event). However, no cases of dosing errors based on variability in the assays used during treatment monitoring of FIX levels have been reported from the rIX-FP clinical development program or from post-marketing experience. This could be due to underreporting. However, section 4.2 includes a detailed section on treatment monitoring, which is considered sufficient. Removal of the potential risk is accepted. Medication errors should continue to be monitored in the PSUR.

**Missing information:**

- **Experience in patients with severe renal and hepatic impairment**

**Historical reason/ perspective for inclusion:**

Subjects with hepatic impairment were specifically excluded from clinical trials for rIX-FP if aspartate aminotransferase or alanine transaminase were > 5 times the upper limit of normal. Therefore, information on use of rIX-FP in patients with severe hepatic impairment was considered as missing information.

Subjects with renal impairment were specifically excluded from clinical trials for rIX-FP if serum creatinine > 2 times the upper limit of normal at screening. Therefore, information on use of rIX-FP in patients with severe renal impairment was considered as missing information.

*Reason for proposed removal:*

rIX-FP is similar to naturally occurring proteins in the human body (ie, FIX and albumin) so no deleterious effects are expected in patients with hepatic and renal impairment. Additionally, it is noted in the product labeling that rIX-FP is a prescription only medicine which is expected to be used under the supervision of a physician experienced in the treatment of hemophilia B.

Cumulatively, 11 case reports (all pertaining to rIX-FP) were received from post-marketing experience, all in patients with medical history of Hepatitis C; Of these, 3 patients additionally reported Hepatitis B, Hepatic cirrhosis, and Hepatic fibrosis, respectively. Review of the post-marketing safety data indicates that patients with hepatic impairment have been prescribed rIX-FP, with no new safety concerns identified to date specific to this special population.

Cumulatively, 3 case reports (2 pertaining to rIX-FP and 1 to generic FIX) with pre-existing renal condition were received from post-marketing experience where CSL Behring assessed that none of these conditions were considered as severe renal impairment.

Overall, the available evidence from post-marketing experience indicates that the safety profile of rIX-FP in patients with severe hepatic and renal impairment is not different from the population studied in clinical trials and use in the post-marketing setting to date. Hence, no specific safety risk is anticipated in these populations and the lack of information alone does not warrant the inclusion as a safety concern. Routine monitoring of post-marketing data in these special populations is considered sufficient to gather information to further characterise the nature, severity, and risk of adverse outcomes associated with rIX-FP use in patients with severe hepatic and renal impairment.

***PRAC Rapporteur assessor's comment:***

Experience in patients with severe renal and hepatic impairment as missing information is accepted for removal since cumulative and recent data (last PSUR) indicate that events developing from renal or hepatic impairment are mostly related to underlying medical condition. Although these populations were not included in clinical trials, a different safety profile for rIX-FP in patients with renal or hepatic impairment is currently not expected. The MAH should include this population for monitoring in the PSUR for further evaluation.

- ***Efficacy and Safety in PUPs***

*Historical reason/ perspective for inclusion:*

Since the inclusion criteria for the pivotal rIX-FP Clin Dev program required previous FIX treatment, information on efficacy and safety in PUPs was considered as missing information for rIX-FP at the time of the initial marketing authorization in the EU.

*Reason for proposed removal:*

Study CSL654\_3003 that enrolled both PTPs (Arms 1-3) and PUPs (Arm 4) has now been completed. During the study, 12 PUPs (all < 6 years of age except 1 subject of 11 years of age) received  $\geq 1$  dose of rIX-FP. The efficacy data reported for PUPs was consistent with those previously reported for PTPs and confirmed that rIX-FP is effective as routine prophylaxis and as on-demand treatment in pediatric PUPs  $\leq 12$  years at the currently approved dosing regimens.

One PUP previously treated with blood products prior to enrollment in the study developed an inhibitor to FIX. There were no deaths, serious hypersensitivity reactions, anaphylaxis, non-neutralizing antibodies to

FIX, TEEs or antibodies to CHO host cell proteins that were reported in the study. One nonserious TEAE of Hypersensitivity (associated with the FIX inhibitor) led to discontinuation of study treatment. Overall, no safety concerns were identified in PUPs over up to 3 years of rIX-FP treatment.

Cumulatively, there are no reports of inhibitor development in PUPs from post-marketing experience to date.

Overall, the safety and efficacy of rIX-FP in PUPs is consistent with the known safety and efficacy profile of rIX-FP in adult and pediatric PTPs with hemophilia B reported previously and this is reflected in the updated product labeling. Routine monitoring of post-marketing data along with review of inhibitor development against FIX as an important identified risk for rIX-FP are considered sufficient to gather additional information regarding the use of rIX-FP in PUPs and to further identify any potential adverse outcomes associated with rIX-FP.

***PRAC Rapporteur assessor's comment:***

Efficacy and safety of rIX-FP have been investigated in study 3003 for 12 PUPs. There were no SEAs except for development of inhibitor to FIX and consequently hypersensitivity reactions, which are known identified risks. No new safety concerns were identified in this population and no other safety profile is expected. Accepted for removal.

- ***Experience in pregnancy and lactation, including labour and delivery***

***Historical reason/ perspective for inclusion:***

Hemophilia B is an X-chromosome linked recessive disorder, therefore it is more common in men (87%) than in women (5%) and unknown gender (6%) [WFH Global Survey, 2020]. The clinical studies for rIX-FP enrolled only males, as such information regarding the use of rIX-FP in pregnancy and lactation was considered as missing information.

***Reason for proposed removal:***

rIX-FP is similar to naturally occurring proteins in the human body (i.e., FIX and albumin) so no effects on embryo-toxicity and fertility are expected. Additionally, recommendations are included in the product labeling to only use rIX-FP during pregnancy and lactation when clearly indicated and for caution to be exercised during administration to a nursing mother.

Cumulatively, there was only 1 non-serious pregnancy case report from post-marketing experience where a female patient who was a hemophilia B carrier was given rIX-FP before vaginal delivery. The pregnancy outcome was normal with no post-delivery complications for both the mother and child.

There are no literature articles reporting safety concerns of use of FIX products in pregnancy and lactation to date. There are no literature articles reporting use of rIX-FP in pregnancy and lactation to date.

Overall, there is no data to suggest that the safety profile is different in pregnant or breastfeeding females and sufficient guidance is provided in the product labeling. Hence, no specific safety risk is anticipated in these populations and the lack of information alone does not warrant the inclusion as a safety concern. Routine monitoring of post-marketing data together with pregnancy experience, and outcome questionnaires, and information noted in the product labeling are considered sufficient to gather further information regarding any potential adverse outcomes associated with use of rIX-FP in pregnancy and lactation.

**PRAC Rapporteur assessor's comment:**

The MAH has indicated that cumulatively there is only 1 pregnancy case report from post-marketing experience. A single pregnancy case is not considered sufficient to characterize experience in pregnancy and lactation. The issue should remain in the summary of safety concerns together with the routine pharmacovigilance activity of a specific follow-up questionnaire to further characterize the risk.

- **Experience in elderly patients**

Historical reason/ perspective for inclusion:

Elderly patients (> 65 years of age) were excluded from the clinical trial program for rIX-FP. From the data obtained in the worldwide literature to date, there is a paucity of information regarding use of rIX-FP in individuals over 65 years of age.

Reason for proposed removal:

rIX-FP is similar to naturally occurring proteins in the human body (ie, FIX and albumin) so no deleterious effects are expected in this patient population.

Cumulatively, 14 cases were reported for rIX-FP in the post-marketing experience from patients aged older than 65 years of which, 4 patients were aged between 65 to 69 years, 5 patients were aged between 70 to 79 years, 1 patient was aged between 80 to 89 years, and for 4 patients the age was not reported. The most reported AEs were mostly bleeding events (Gingival bleeding/ Haemorrhage/ Haemorrhoidal haemorrhage/ Muscle haemorrhage/ Haemarthrosis) due to the underlying condition, and the only related AE was Drug ineffective (reported in 5 patients). Review of these cases did not identify any safety relevant information specific to this age group.

Overall, the safety data obtained from post-marketing use in elderly patients is in line with the safety profile of the product as established in clinical studies and by post-marketing surveillance and there is no indication of a specific safety risk in elderly patients. Hence, no specific safety risk is anticipated in this age group and the lack of information alone does not warrant the inclusion as a safety concern. Routine monitoring of post-marketing data in this age group is considered sufficient to gather further information regarding any potential adverse outcomes associated with rIX-FP use in elderly patients.

**PRAC Rapporteur assessor's comment:**

Experience in elderly should remain as missing information in the summary of safety concerns as safety in this population is yet not considered adequately characterized. The last PSUR shows that cases of elderly are reported but lacked sufficient information for further assessment. Although no safety information could be identified, the risk should be further monitored in the PSUR. In addition, this population is part of participation in EUHASS to collect long-term safety data (additional pharmacovigilance activity).

- **Experience in patients for ITI (off-label use)**

Historical reason/ perspective for inclusion:

Immune tolerance induction (ITI) has been an off-label practice for FIX products to treat inhibitor development based on published literature [Klamroth et al, 2019; Roberts et al, 2019; Saini et al, 2019; Ahmad-Nabi et al, 2018; Malec et al, 2018; Verghese et al, 2013]. The goal of ITI is eradication of inhibitors to restore responsiveness to FIX treatment. ITI eliminates the anamnestic response by administering high doses of FIX. Treatment regimens utilize ongoing, frequent, uninterrupted exposure to FIX over a period of a few months to 2 or more years with the goal of inducing antigen-specific tolerance. Successful ITI leads to normalization of the FIX half-life, near normalization of the patient's quality of life, and a marked reduction in treatment costs over the long term.



ITI was not part of the Clin Dev program for rIX-FP. Information on off-label use for ITI was thus classified as missing information with an aim to quantify the extent of off label use and further characterize the risk to inform health care professionals about the unknown benefit- risk profile of rFIX-FP in ITI.

**Reason for proposed removal:**

There are no reports of use of rIX-FP for ITI from post-marketing experience to date. There are no literature articles reporting use of rIX-FP for ITI to date. There have been literature reports of nephrotic syndrome following ITI therapy with other FIX products [Ahmad-Nabi et al, 2018; Malec et al, 2018; Verghese et al, 2013].

Overall, there is no evidence of this risk being different to other FIX products. The product labeling advises that the safety and efficacy has not been established in ITI therapy and about risk in patients with history of allergic reactions. It also specifically advises on nephrotic syndrome following attempts with ITI in patients with a history of allergic reactions and FIX inhibitors. Additionally, routine monitoring of post-marketing data for off-label use of ITI therapy and hypersensitivity and inhibitors to factor IX (important identified risks for IX- FP) is considered sufficient.

***PRAC Rapporteur assessor's comment:***

It is acknowledged that from post-marketing experience no reports of use of rIX-FP for ITI have been received. ITI has not been part of the Clin Dev program for rIX-FP and there is currently insufficient evidence regarding this risk of off-label use. Nonetheless, a different safety profile is not expected and therefore Experience in patients for ITI (off-label use) is accepted to remove as missing information from the summary of safety concerns. The risk should be followed with routine pharmacovigilance activities and need to be monitored through PSURs.

***PRAC Rapporteur assessor's comment:***

Overall, the summary of safety concerns should be updated to:

**Important identified risks**

- Hypersensitivity / anaphylactic reactions
- Development of inhibitors to factor IX

**Important potential risks**

- TEEs

**Missing information**

- Experience in pregnancy and lactation, including labour and delivery
- Experience in elderly patients

## 9.2. Pharmacovigilance plan

### Routine pharmacovigilance activities

Routine PV activities are in place. In addition, the RMP has specific adverse reaction follow-up questionnaires for important identified risks of Hypersensitivity / anaphylactic reactions and Thromboembolic events

#### **PRAC Rapporteur assessor's comment:**

The FU-Q for missing information of Experience in pregnancy and pregnancy outcomes was removed, which is not accepted since experience in pregnancy and lactation should remain missing information, for which a FU-Q is warranted.

### Additional pharmacovigilance activities

The description on study CSL654\_3003 was deleted. The other additional PhV activity remains in place, i.e.; Hemophilia Network Registry: European Haemophilia Safety Surveillance (EUHASS) - To obtain long-term safety data (including inhibitor development) and to review the data for safety concerns.

**Table Part III.3-1: On-going and planned additional pharmacovigilance activities**

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
<b>Category 3</b> - Required additional pharmacovigilance activities				
Participation in EUHASS to collect long-term safety data.  Ongoing	To obtain and review long term available post-marketing data for safety concerns	Hypersensitivity /anaphylactic reactions • Development of inhibitors to factor IX • TEEs	Scheduled periodic report from EUHASS	Interim updates based on EUHASS reports will be included in each PSUR.

### Plans for post-authorization efficacy studies

The MAH proposed to remove of table IV.1 for study CSL654\_3003

#### **PRAC Rapporteur assessor's comment:**

Removal of study CSL654\_3003 from additional pharmacovigilance activities can be accepted since the study has been finalized. The summary table (III.3-1) is in line with the pharmacovigilance plan. However, the additional pharmacovigilance activities should include safety concerns addressed "Usage and safety in the elderly ( $\geq 65$  years)" as was stated in RMP version 3.4. Overall, this section should be updated in accordance with the summary of safety concerns.

## 9.3. Risk minimization measures

#### **PRAC Rapporteur assessor's comment:**

Table Part V.1-1 and V.3-1 were aligned with removal of the safety concerns. This section should be updated in accordance with the summary of safety concerns.

#### **9.4. Overall conclusion on the RMP**

☒ With the responses to 2<sup>nd</sup> Request for Supplementary information the MAH submitted an updated RMP (version 4.1) which is considered acceptable.

### **10. Changes to the Product Information**

As a result of this variation, sections 4.2, 4.8, 5.1 of the SmPC have been updated based on the final results from study CSL654\_3003 listed as a category 3 study in the RMP. The package Leaflet has been amended, accordingly.

## **11. Request for supplementary information**

### **11.1. Major objections**

None.

### **11.2. Other concerns**

#### ***Clinical aspects***

General:

1. The MAH is asked to submit the final PIP Compliance Report.
2. The MAH is asked to verify the number of patients with severe Haemophilia B (<1% FIX activity) and provide respective patient-related data.
3. One 11-year-old subject was included. In patients with severe haemophilia it is not plausible that no factor-replacement has been administered up to this age. Clinical details beyond the provided case-narrative regarding history, and haemophilia-type and -severity of this patient should be amended for better understanding. Of note, this patient developed high-titre inhibitor with hypersensitivity, and was the only patient with Asian ethnicity.

Pharmacokinetics:

4. The only patient within the older paediatric age group (11 years) had untypical significantly lower IR and cmax values, and did not reach measurable steady-state results. These conflicting PK- and zero-trough-level-results should be discussed with respect to the clinical/timely context of the evaluation with inhibitor-development in this patient.
5. The number of patients with true severe Haemophilia B (<1% FIX activity) and – if appropriate, subgroup PK-analysis of only these data-sets should be amended for further discussion and reflection in the Clinical Overview.
6. Time on study: Min and Max values of the “Total” patient collective in the last column of Table 10-3, CSR, cannot be traced from the values of the reference columns. The MAH is asked to explain.

Efficacy:

7. Total Annualized Bleeding Rates (ABRs) for all subjects having received >6 months of prophylaxis, and individual ABR together with individual treatment duration are requested.
8. According to the Clinical Guideline, consumption should be presented for prophylaxis as dose per kg per month and year for patients on prophylaxis for >6 months, and for on-demand treatment as dose per kg per event (bleeding episode). For on-demand treatments, the dose per kg per bleeding event should be available at least for all bleeds (total), spontaneous, and traumatic bleeds. Data should be presented as median and range.
9. According to the Clinical Guideline, treatment response should be presented as “none”, “moderate”, “good” or “excellent”. Treatment response of all 37 bleeding episodes (spontaneous, traumatic, and of unknown cause) should be amended that way.

Surgery:

10. One subject entered the surgery substudy for port insertion for a “surgery period” of 8 days. Total consumption per kg and surgical procedure, and additional information is requested, according to the Clinical Guideline.

2 additional subjects underwent surgical procedures: 1 underwent (1) port insertion and (2) bilateral ear-tube-insertion. 1 patient underwent revision of sagittal suture craniosynostosis. The latter surgery is considered major. Data on total consumption per kg and surgical procedure is requested for both additional subjects, as far as available.

#### Safety:

11. Presentation of all potential hypersensitivity reactions in the CSR is divergent: Section 12.3.1 describes 9 “hypersensitivity reactions; Table 12-3 displays 2 events of urticaria, and 4 events of rash; Table 12-4 displays 3 “hypersensitivities” within 72 hours; Table 12-6 (SMQ search) displays 9 “hypersensitivities”, 4 “rashes”, and 2 “urticarias”. Brief and meaningful presentation of this clinically relevant entity of events is requested.
12. At least one subject experienced an SAE of “Device Related Infection”. All device related complications (including non-serious) should be presented, irrespective of causal relation.

#### Clinical Overview:

13. Clinical Overview should be updated according to the assessment for presenting meaningful data. PK-results should be presented as median and range. Key efficacy and safety data should be amended according to the assessment. Presentation of inhibitor development should rely on those (6) subjects with  $\geq 50$  EDs. Further, other significant events including hypersensitivities and device-related complications should be addressed, adequately.

#### SmPC:

14. Substantial abbreviation of the proposed SmPC-amendments is requested, according to the assessment and to the comments made in the attached product information (please, refer to Attachment 1).

### ***RMP aspects***

15. The MAH should update the summary of safety concerns to:

#### Important identified risks

- Hypersensitivity / anaphylactic reactions
- Development of inhibitors to factor IX

#### Important potential risks

- TEEs

#### Missing information

- Experience in pregnancy and lactation, including labour and delivery
- Experience in elderly patients

16. The MAH should include “patients with severe renal and hepatic impairment”, “medication errors” and “Experience in patients for ITI (off-label use)” for monitoring in the PSUR for further evaluation.
17. The FU-Q for missing information of Experience in pregnancy and pregnancy outcomes should remain as routine pharmacovigilance activity.
18. The elderly population (>65 years) should remain part of participation in EUHASS to collect long-term safety data (additional pharmacovigilance activity).

## **12. Assessment of the responses to the request for supplementary information**

### **12.1. Other concerns**

#### ***Clinical aspects***

##### General:

##### **Question 1**

The MAH is asked to submit the final PIP Compliance Report.

##### **Summary of the MAH's response**

The final PIP Compliance Report (C-001107-PIP-01-10-M04) has been provided in Module 1.10 with this response to the request for supplementary information.

##### **Assessment and Conclusion: Point is solved**

##### **Question 2**

The MAH is asked to verify the number of patients with severe Haemophilia B (<1% FIX activity) and provide respective patient-related data.

##### **Summary of the MAH's response**

In response to the rapporteur's request, CSLB first evaluated all central laboratory values before PK dosing. For those central laboratory values  $\geq 1\%$ , all available FIX activity data (local laboratory) including case report forms (CRFs) were checked. In case of missing values, CSLB also followed up with Principal Investigators to confirm hemophilia B severity. Across these sources of information (summarized in Table 1), CSLB confirms that all 12 treated PUPs in Study CSL654\_3003 have severe hemophilia B (< 1% FIX activity).

**Table 1 Summary of Information Relevant to Hemophilia B Severity (CSL654\_3003 PUP)**

	Predose PK FIX activity (central lab) [%]	FIX activity in CRF before first dose (local lab) [%]	Follow-up information from Principal Investigator
	3.4	0.6	
	0.9		
	0 <sup>a</sup>		
	2.3		Severe hemophilia B confirmed by investigator email [21 JUN 2022 ])
	Not done	0.54	
	0 <sup>a</sup>		
	20.2 <sup>b</sup>	< 1	
	0 <sup>a</sup>		
	1.7		Severe hemophilia B confirmed by investigator email [13 JUN 2022])
	0 <sup>a</sup>		
	Not collected		Severe hemophilia B confirmed by investigator email [15 JUN 2022])
	0 <sup>a</sup>		

CRF = case report form; FIX = factor IX; ID = identification; PK = pharmacokinetics; PUP = previously untreated patient.

<sup>a</sup> Below the quantification limit of 0.2%.

<sup>b</sup> PK evaluation in this subject was done in March 2017 during the study, not as the first dose (in August 2015). The subject received prophylaxis treatment during the study, and the washout period was not sufficient for FIX levels to return to baseline.

Sources: CSL654\_3003 PUP CSR [Listing 16.2.5.5.1.99](#); case report forms; follow-up communication with Principal Investigators.

### Assessment of the MAH's response

12 of 12 included PUPs were confirmed to suffer from severe Hemophilia B, either confirmed by laboratory values from this study, or confirmed by investigator email.

**Conclusion: Point is solved.**

### Question 3

One 11-year-old subject was included. In patients with severe haemophilia it is not plausible that no factor-replacement has been administered up to this age. Clinical details beyond the provided case-narrative regarding history, and haemophilia-type and -severity of this patient should be amended for better understanding. Of note, this patient developed high-titre inhibitor with hypersensitivity, and was the only patient with Asian ethnicity.

### Summary of the MAH's response

CSLB has contacted the principal investigator (PI) of the investigational site and asked for additional information on the medical history of the patient. The medical records of the patient did not contain any new information besides the provided information in the narrative (CSL654\_3003 PUP CSR Section 14.3.3.2). The PI decided to contact both patient and his parents and asked for additional information.

On 26 October 2011 and 30 October 2011 the subject had received transfusions with packed red blood cells (1 administration on each day) for the treatment of anemia associated with a violaceous scrotal swelling 3 to 4 days after circumcision. He was also treated with tranexamic acid at that time. After a week, the swelling subsided. The subject had a negative family history of bleeding disorders. At that time the family physician had suspicion raised for a non-specific bleeding disorder. He advised for a referral to a pediatric hematologist but the parents decided not to consult a hematologist until 2013. Severe hemophilia B (< 1%) was diagnosed on 9 July 2013 after a factor assay was requested by a referred hematologist. After diagnosis of hemophilia B the parents only noticed isolated ecchymosis in trauma-induced areas. Parents recalled that he had these events before the diagnosis and attributed these to the high activity status of the child. Spontaneous resolution of ecchymosis were noticed and no factor replacement was given of either plasma products or factor concentrates. No further medical history or prior medications related to hemophilia or other treatments prior to study enrollment were reported other than that of circumcision. In 2015 he was referred to the investigational site, enrolled into the study and treated with rIX-FP as described in the patient's narrative (CSL654\_3003 PUP CSR Section 14.3.3.2).

The PI further remarked that comprehensive hemophilia care is relatively new in the Philippines. The diagnosis is usually late and most just presumptive through medical history of hemophilia in the family or maternal male relatives. Factor assays are not widely available in every region in the country and are expensive. Hemophilia Factor IX concentrates are not commercially available in the Philippines. Sometimes they are donated from international hemophilia organizations.

### Assessment of the MAH's response

Additional information regarding the patient's history, and the medicinal background have been provided. This amendment further enlightens the specific circumstances, explaining why a patient with severe Haemophilia B (<1% FIX activity) has been treated with a factor concentrate the first time in his life at the age of 11. The circumstances of medical care, clearly deviating from Western European Countries may serve as an acceptable explanation for the unusual history.

### Conclusion: Point is solved



## Pharmacokinetics:

### Question 4

The only patient within the older paediatric age group (11 years) had untypical significantly lower IR and Cmax values, and did not reach measurable steady-state results. These conflicting PK- and zero-trough-level-results results should be discussed with respect to the clinical/timely context of the evaluation with inhibitor-development in this patient.

### Summary of the MAH's response

One patient had baseline-corrected IR and Cmax values of 0.8 [IU/dL]/[IU/kg] and 39.9 IU/dL, respectively. These values are slightly lower than the minimum values in the < 6 years age group (0.9 [IU/dL]/[IU/kg] and 45.2 IU/dL, respectively). For comparison, as shown in Section 5.2 of the IDELVION SmPC, the minimum values of IR and Cmax in previously treated patients (PTPs) 6 to < 12 years of age were 0.7 [IU/dL]/[IU/kg] and 34.9 IU/dL, respectively. Therefore, while this PUP had the lowest IR and Cmax values in the PUP arm, these values are within the same ranges as those in the same age group in previous studies.

Additionally, the lack of steady-state results for this PUP is not due to values below the level of quantification, but because this PUP did not have any FIX activity samples that met the trough or steady-state requirements. As all of his PK samples were collected at unscheduled visits (except for 1 which was collected 5 days after rIX-FP administration), none could be classified as trough or steady-state levels.

The timeline of FIX activity and inhibitor assessments for this PUP up to and including inhibitor detection is summarized in Table 2. The complete data for inhibitor titer over time are available in CSL654\_3003 PUP CSR Listing 16.2.8.1.4.1.99.

**Table 2 Subject 6080001-3002: FIX Activity and Inhibitor Assessments (CSL654\_3003 PUP)**

Date	Visit	Test	Value
28 March 2015	Screening	FIX inhibitor	< 0.4 BU
24 April 2015	PK Period Day 1	FIX inhibitor	< 0.4 BU
		FIX predose	BQL
		FIX 30 minutes postdose	39.9 IU/mL
27 April 2015	PK Period Day 3	FIX 72 hours postdose	16.3 IU/mL
30 April 2015	PK Period Day 7	FIX 168 hours postdose	6.3 IU/mL
20 May 2015	Month 1	FIX inhibitor	< 0.4 BU
		FIX (5 days postdose)	12.0 IU/mL
17 June 2015	Month 2	FIX inhibitor	0.58 BU
14 July 2015	Month 3	FIX inhibitor	3.37 BU
31 July 2015	Unscheduled	FIX inhibitor	5.61 BU

BU = Bethesda units; BQL = below quantifiable limit; FIX = factor IX; PK = pharmacokinetics; PUP = previously untreated patient.

Source: CSL654\_3003 PUP CSR Listing 16.2.5.5.1.99 (FIX activity), Listing 16.2.8.1.4.1.99 (FIX inhibitor), Listing 16.2.5.7.1.99 (observed and steady-state FIX activity).

### Assessment of the MAH's response

Further details have been provided regarding the child who presented exceptional patient's characteristics and laboratory results. Presented data are considered to be plausible.

### Conclusion: Point is solved.

### Question 5

The number of patients with true severe Haemophilia B (<1% FIX activity) and – if appropriate, subgroup PK-analysis of only these data-sets should be amended for further discussion and reflection in the Clinical Overview.

### Summary of the MAH's response

Severe hemophilia B has been confirmed for all 12 PUPs (see Response to Question 2). Thus, additional subgroup analyses (requested by the reviewer in Question 5) are not necessary, and the Clinical Overview was not amended with an additional subgroup analysis.

### Assessment and Conclusion: Point is solved

### Question 6

Time on study: Min and Max values of the "Total" patient collective in the last column of Table 10-3, CSR, cannot be traced from the values of the reference columns. The MAH is asked to explain.

### Summary of the MAH's response

In-text Table 10-3 of the CSR for time on study is provided for reference; the Min and Max values in the last column ("Total" study duration) are highlighted:

<b>Table 10-3 Time on Study, by Study Period (PUP Safety Population, Arm 4)</b>						
<b>Parameter</b>	<b>On-demand Period N = 6</b>	<b>Prophylaxis Regimen</b>			<b>Intensified Treatment<sup>a</sup> N = 1</b>	<b>Total N = 12</b>
		<b>7-Day N = 11</b>	<b>10-Day N = 1</b>	<b>Total N = 12</b>		
Time on period, months						
Mean (SD)	8.91 (4.177)	15.52 (10.275)	12.12 (NA)	15.24 (9.845)	20.24 (NA)	21.38 (8.029)
Median (min, max)	10.79 (1.9, 12.3)	10.87 (3.1, 32.3)	12.12 (NA)	11.50 (3.1, 32.3)	20.24 (NA)	22.65 (4.5, 33.0)
Time on period, weeks						
Mean (SD)	38.74 (18.162)	67.49 (44.676)	52.71 (NA)	66.26 (42.810)	88.0 (NA)	92.96 (34.912)
Median (min, max)	46.93 (8.3, 53.6)	47.29 (13.4, 140.3)	52.71 (NA)	50.00 (13.4, 140.3)	88.0 (NA)	98.50 (19.6, 143.4)

max = maximum; min = minimum; NA = not applicable; PUP = previously untreated patient.

Note: Analysis excludes the exposure in the PK and surgery periods.

<sup>a</sup> One PUP developed inhibitor to FIX. A case narrative for this PUP is available in [Section 14.3.3.2](#).

Source: CSL654\_3003 PUP CSR, [Table 14.1.4.2.1.99](#)

CSLB was asked to explain why the Min and Max values in the last column ("Total") representing all subjects and all time periods are not reflected in the columns by study period or treatment regimen. For example, the minimum time on study is given as 4.5 months in the "Total" column, while the minimum time on study is shown as 1.9 months in the On-demand Period and 3.1 months during the 7-day prophylaxis regimen; both values in the study period columns are lower than in the "Total" column.

The reason is that values in the "Total" column are derived subject-level data and are the sum of the durations across all regimen periods for each subject. As seen in Listing 1, for example:

- One subject (marked in bold) had a study duration of 1.9 months in the On-demand Period and 31.1 months on the 7-day regimen. Although 1.9 months is the minimum value for the On-demand Period of all subjects who had an On-demand Period, it does not appear in the "Total" study duration column, because total duration for this subject was approximately 33 months (ie, On-demand + 7-day regimen).
- The minimum value in the "Total" column (4.5 months) comes from one subject (italics). In contrast, the minimum value in the "7-day regimen" column SR Table 10-3 is due to one subject (italics).

**Listing 1 Time on Period in Months (PUP Safety Population, Arm 4)**

On-demand Period	7-Day Regimen	10-Day Regimen	Intensified Treatment	Total
12.3	10.4			22.7
11.8	9.7			21.5
5.8	7.9			13.7
	21.9			21.9
		12.1		12.1
	24.2			24.2
	32.3			32.3
	3.1		20.2	23.3
<b>1.9</b>	<b>31.1</b>			<b>33.0</b>
	4.5			4.5
9.9	14.9			24.7
11.7	10.9			22.6

PUP = previously untreated patient.

Source: CSL654\_3003 PUP CSR, Listing 16.2.5.3.1.99

### Assessment of the MAH's response

Meaning of the "Total" column for respective time-periods of treatment has been explained by the MAH to be subject-level data and the sum of the durations across all regimen periods for each subject. This explanation is taken.

### Conclusion: Point is solved

#### Efficacy:

#### Question 7

Total Annualized Bleeding Rates (ABRs) for all subjects having received >6 months of prophylaxis, and individual ABR together with individual treatment duration are requested.

### Summary of the MAH's response

Ten of the 12 PUPs received > 6 months of prophylaxis with rIX-FP. On the 7-day regimen (N = 9), median ABR was 0 (0 to 1.5) for treated bleeding episodes and 1.16 (0 to 3.1) for all bleeding episodes. Data are provided in Table 3 (individual ABRs and treatment durations) and Table 4 (ABR summary statistics for treated and all bleeding episodes).

Section 2.5.4.2.1.1 of the Clinical Overview has been amended to reflect this information.

**Table 3 Total Annualized Bleeding Rates for Subjects on Prophylaxis Treatment for > 6 Months (> 183 Days) (CSL654\_3003 PUP)**

Period		Bleeding Episodes		ABR	
Regimen/ Start Date	Duration [Days] <sup>a</sup>	Treated	Nontreated	Treated	All
7-Day	316	0	1	0.00	1.16
7-Day	296	0	0	0.00	0.00
7-Day	239	0	2	0.00	3.06
7-Day	667	2	0	1.10	1.10
10-Day	369	1	0	0.99	0.99
7-Day	737	2	1	0.99	1.49
7-Day	982	4	2	1.49	2.23
7-Day	946	4	0	1.54	1.54
7-Day	452	0	0	0.00	0.00
7-Day	331	0	0	0.00	0.00

ABR =annualized bleeding rate; ID = identification; PUP = previously untreated patients.

Note: Only bleeding events during prophylaxis period that occurred after dosing on or after the start date of period are counted.

<sup>a</sup> Duration of treatment period (days) = (end of treatment period date - start of treatment period date + 1).

Source: CSL654\_3003 PUP Ad hoc tables 22 Jun 2022, [Listing 7a](#)

**Table 4 Summary of Total Annualized Bleeding Rates for Subjects on Prophylaxis Treatment for > 6 Months (> 183 Days) (CSL654\_3003 PUP)**

	ABRs Based on Treated Bleeding Episodes	ABRs Based on All Bleeding Episodes
<b>7-Day Regimen (N = 9)</b>		
n	9	9
Mean (SD)	0.57 (0.695)	1.17 (1.063)
Median	0.00	1.16
Min, Max	0.0, 1.5	0.0, 3.1
<b>10-Day Regimen (N = 1)</b>		
n	1	1
Mean (SD)	0.99 (NC)	0.99 (NC)
Median	0.99	0.99
Min, Max	1.0, 1.0	1.0, 1.0
<b>Total (N = 10)</b>		
n	10	10
Mean (SD)	0.61 (0.669)	1.16 (1.004)
Median	0.49	1.13
Min, Max	0.0, 1.5	0.0, 3.1

ABR =annualized bleeding rate; N, n = number of subjects; NC = not calculable; PUP = previously untreated patients.

Source: CSL654\_3003 PUP Ad hoc tables 22 Jun 2022, [Table 7b](#)

### Assessment of the MAH's response

The MAH presented data on ABRs in patients on treatment for more than 6 months as requested by the Clinical Guideline. Further, a differentiation between "treated" bleeds and "all" bleeds has been evaluated. The context according to the assessment was the presentation of "spontaneous" bleeds with a rate of zero – "spontaneous" bleeds being no standardized and relevant term. However, the now presented data are considered to adequately describe the efficacy in the treated patient population.

### Conclusion: Point is solved

### Question 8

According to the Clinical Guideline, consumption should be presented for prophylaxis as dose per kg per month and year for patients on prophylaxis for >6 months, and for on-demand treatment as dose per kg per event (bleeding episode). For on-demand treatments, the dose per kg per bleeding event should be available at least for all bleeds (total), spontaneous, and traumatic bleeds. Data should be presented as median and range.

### Summary of the MAH's response

The requested data are provided in Table 5 (prophylaxis) and Table 6 (on-demand). Section 2.5.4.2.1.2 of the Clinical Overview has been amended accordingly.

**Table 5 Consumption of rIX-FP as Prophylaxis Treatment for Subjects on Prophylaxis Treatment for > 6 Months (> 183 Days) (CSL654\_3003 PUP)**

	7-Day Regimen (N = 9)	10-Day Regimen (N = 1)	Total (N = 10)
<b>Monthly Dose (IU/kg)</b>			
n	9	1	10
Median	195.90	132.10	192.50
Min, Max	171.8, 215.6	132.1, 132.1	132.1, 215.6
<b>Yearly Dose (IU/kg)</b>			
n	9	1	10
Median	2350.70	1584.80	2309.70
Min, Max	2062.1, 2587.1	1584.8, 1584.8	1584.8, 2587.1

N, n = number of subjects; PUP = previously untreated patients.

Note: Consumption of rIX-FP in this table includes all doses administrated during prophylaxis periods.

Source: CSL654\_3003 PUP Ad hoc tables 22 Jun 2022, [Table 8a](#)

**Table 6 Consumption of rIX-FP as On-demand Treatment for Bleeding Episodes (CSL654\_3003 PUP)**

	On-demand Period	7-Day Regimen Period	10-Day Regimen Period	Total
<b>Number of Subjects with Treated Bleeding Episodes</b>				
	4	6	1	10
<b>Number of Treated Bleeding Episodes</b>				
	6	14	1	21
<b>Dose [IU/kg] per Bleeding Episode (Total)</b>				
e	6	14	1	21
Median	50.20	57.60	50.00	50.40
Min, Max	34.0, 102.0	35.2, 303.6	50.0, 50.0	34.0, 303.6
<b>Dose [IU/kg] per Bleeding Episode (Spontaneous)</b>				
e	1	4	0	5
Median	50.40	77.90	N/A	64.20
Min, Max	50.4, 50.4	49.9, 100.4	N/A	49.9, 100.4
<b>Dose [IU/kg] per Bleeding Episode (Traumatic)</b>				
e	5	9	1	15
Median	50.00	51.00	50.00	50.20
Min, Max	34.0, 102.0	47.4, 303.6	50.0, 50.0	34.0, 303.6
<b>Dose [IU/kg] per Bleeding Episode (Unknown)</b>				
n	0	1	0	1
Median	N/A	35.20	N/A	35.20
Min, Max	N/A	35.2, 35.2	N/A	35.2, 35.2

e = number of bleeding episodes; N/A = not applicable; PUP = previously untreated patients.

Source: CSL654\_3003 PUP Ad hoc tables 22 Jun 2022, [Table 8b](#)

### Assessment of the MAH's response

The MAH submitted the requested evaluations on efficacy.

Yearly consumption for prophylaxis was about 2900 IU/kg with wide interindividual variability based upon only 10 individuals. Distinction for 7-days- or 10-days- regimens is not possible due to the low numbers of 9 and 1 individuals, respectively. Overall, the consumption is within the frame of similar replacement products.

Dose per bleeding episode in on-demand patients has been presented for all bleeding episodes, spontaneous, traumatic and "unknown" bleeds. Overall, doses are considered to represent plausible values, although evaluation is again challenged by low numbers, overall.

### Conclusion: Point is solved



## Question 9

According to the Clinical Guideline, treatment response should be presented as “none”, “moderate”, “good” or “excellent”. Treatment response of all 37 bleeding episodes (spontaneous, traumatic, and of unknown cause) should be amended that way.

## Summary of the MAH’s response

There were no major bleeding episodes in PUPs.

Treatment response data are available for 13 of the 37 nonmajor bleeding episodes (see summary in Table 7). The investigators assessed treatment response as “excellent” or “good” for all these 13 minor bleeding episodes. The missing data can be ascribed to the fact that treatment response was not consistently assessed and / or recorded, because bleeding episodes were minor, most were treated at home during the prophylaxis period, and PUPs / caregivers did not need to visit the study site at the time of the bleeding episode. Section 2.5.4.2.2 of the Clinical Overview has been amended accordingly.

**Table 7 Treatment Response for Minor Bleeding Events Treated with CSL654, by Regimen and Bleeding Event Type (CSL654\_3003 PUP)**

Bleeding Event Type	On-demand Regimen (N=4)	7-Day Regimen (N=6)	10-Day Regimen (N=1)	Intensified Treatment (N=1)	Total (N=10)
<b>Total</b>	6	14	1	16	37
Excellent	4 (66.7)	4 (28.6)	1 (100.0)	0	9 (24.3)
Good	2 (33.3)	2 (14.3)	0	0	4 (10.8)
Moderate	0	0	0	0	0
None	0	0	0	0	0
Missing	0	8 (57.1)	0	16 (100.0)	24 (64.9)
<b>Spontaneous</b>	1	4	0	11	16
Excellent	1 (100.0)	1 (25.0)	0	0	2 (12.5)
Good	0	0	0	0	0
Moderate	0	0	0	0	0
None	0	0	0	0	0
Missing	0	3 (75.0)	0	11 (100.0)	14 (87.5)
<b>Traumatic</b>	5	9	1	2	17
Excellent	3 (60.0)	2 (22.2)	1 (100.0)	0	6 (35.3)
Good	2 (40.0)	2 (22.2)	0	0	4 (23.5)
Moderate	0	0	0	0	0
None	0	0	0	0	0
Missing	0	5 (55.6)	0	2 (100.0)	7 (41.2)
<b>Unknown Cause</b>	0	1	0	3	4
Excellent	0	1 (100.0)	0	0	1 (25.0)
Good	0	0	0	0	0
Moderate	0	0	0	0	0
None	0	0	0	0	0
Missing	0	0	0	3 (100.0)	3 (75.0)

N = number of subjects with treated bleeding episodes, PUP = previously untreated patients.

Table presents number and percentage of treated bleeding episodes. Percentages of total bleeding episodes are based on the number of treated bleeding episodes in PUP Efficacy Population for each study period. Percentage of spontaneous, traumatic, and unknown bleeding episodes are based on the number of treated bleeding episodes for each bleeding type (n) for each study period.

Source: CSL654\_3003 PUP Ad hoc tables 22 Jun 2022 [Table 9a](#); the individual subject data are listed in [Listing 9b](#)

### **Assessment of the MAH's response**

The MAH presented evaluation-data for non-major bleeding episodes as no major bleeds have been recorded, overall. All evaluated bleeding episodes (13 of 37) were rated as excellent or good. No rating for non-major bleeds was mandatory – thus missing data are explained, satisfactorily.

### **Conclusion: Point is solved**

#### Surgery:

#### **Question 10**

One subject entered the surgery substudy for port insertion for a "surgery period" of 8 days. Total consumption per kg and surgical procedure, and additional information is requested, according to the Clinical Guideline.

2 additional subjects underwent surgical procedures: 1 underwent (1) port insertion and (2) bilateral ear-tube-insertion. One underwent revision of sagittal suture craniosynostosis. The latter surgery is considered major. Data on total consumption per kg and surgical procedure is requested for both additional subjects, as far as available.

### **Summary of the MAH's response**

The total consumption for port insertion of Subject who participated in the surgical substudy, was 252 IU/kg administered in 4 doses during the surgical period of 8 days. The estimated blood loss indicated by the investigator before surgery and the actual blood loss during surgical drainage was 5 mL. No transfusion of blood products was reported during the surgical period. No further information was reported by the investigator.

Both Subjects did not participate in the surgical substudy. Subject 0360015-3014 was administered 197.6 IU/kg in 3 doses for port insertion and 147 IU/kg in 2 doses for grommet insertion. Subject was administered > 489.9 IU/kg in 12 doses (amount of 1 dose missing) for sagittal suture craniosynostosis. All available information is listed in amended Listing 10. No transfusions of blood products were reported during the surgical periods.

### **Assessment of the MAH's response**

The MAH submitted additional data on all surgical procedures. Dosages and overall consumption are considered to be plausible, and no transfusions of blood products have been recorded.

### **Conclusion: Point is solved**



## Safety:

### Question 11

Presentation of all potential hypersensitivity reactions in the CSR is divergent: Section 12.3.1 describes 9 “hypersensitivity reactions”; Table 12-3 displays 2 events of urticaria, and 4 events of rash; Table 12-4 displays 3 “hypersensitivities” within 72 hours; Table 12-6 (SMQ search) displays 9 “hypersensitivities”, 4 “rashes”, and 2 “urticarias”. Brief and meaningful presentation of this clinically relevant entity of events is requested.

### Summary of the MAH’s response

Overall, 3 PUPs experienced a total of 9 reactions indicative of hypersensitivity.

**Table 8 Summary of Potential Hypersensitivity Reactions (PUP Safety Population, Arm 4)**

Subject ID Age at Screening	System Organ Class / Preferred Term / Reported Term	Duration (Days) / Serious	Severity <sup>a</sup> / Causal Relationship	Action Taken / Outcome	Within 72 h of rIX-FP
1 year	Skin and subcutaneous tissue disorders/ Rash/ Exanthem	8 / No	Mild / Not related	Dose not changed / Recovered / resolved	No
	Skin and subcutaneous tissue disorders/ Rash/ Exanthem	3 / No	Mild / Not related	Dose not changed / Recovered / resolved	No
1 year	Skin and subcutaneous tissue disorders/ Urticaria/ Urticaria on the whole body	4 / No	Mild / Not related	Dose not changed / Recovered / resolved	No
	Skin and subcutaneous tissue disorders/ Rash/ Skin rash both lower legs and both forearms	4 / No	Mild / Related	Dose not changed / Recovered / resolved	No
	Skin and subcutaneous tissue disorders/ Rash/ Skin rash face and at belly	3 / No	Mild / Not related	Dose not changed / Recovered / resolved	No
	Immune system disorders/ Hypersensitivity/ Hypersensitivity reaction	1 / No	Mild / Related	Drug interrupted / Recovered / resolved	Yes
11 years	Skin and subcutaneous tissue disorders/ Urticaria/ Urticaria	1 / No	Mild / Not related	Drug interrupted / Recovered / resolved	Yes
	Immune system disorders/ Hypersensitivity/ Allergic reaction	1 / No	Mild / Related	Drug interrupted / Recovered / resolved	No
	Immune system disorders/ Hypersensitivity/ Allergic reaction	1 / No	Mild / Related	Drug withdrawn / Recovered / resolved	Yes
	Immune system disorders/ Hypersensitivity/ Allergic reaction	1 / No	Mild / Related	Drug withdrawn / Recovered / resolved	Yes

PUP = previously untreated patient; rIX-FP = recombinant fusion protein linking coagulation factor IX with albumin.

<sup>a</sup> Severity as assessed by the investigator.

Source: CSL654\_3003 PUP CSR Listings 16.2.7.1.2.1.99 and 16.2.1.1.1.99

Safety evaluation of potential hypersensitivity reactions included the analyses of adverse events of special interest (AESIs) and treatment-emergent adverse events (TEAEs), as defined in the clinical study protocol and statistical analysis plan.

AESIs included preferred terms (PTs) associated with the Standardized MedDRA Queries (SMQs) narrow search terms for hypersensitivity. The SMQ of hypersensitivity narrow includes PTs of Hypersensitivity, Rash, and Urticaria. All SMQ findings were subjected to medical review by the sponsor and were assessed for clinical relevance to ensure a comprehensive review of this topic.

In contrast, TEAEs were grouped only by MedDRA system organ class (SOC) and PT, and were not based on SMQs.

Overall, the medical concept of hypersensitivity was described broadly as both AESIs and TEAEs:

Categories	Description	Presentation and Subcategories
1. AESIs	Based on SMQ search	<p><b>All events from SMQ indicative of medical concept hypersensitivity:</b>  PTs of Hypersensitivity (3), Rash (4) and Urticaria (2).  Total of 9 events in 3 subjects. PT of Hypersensitivity occurred only in 1 subject.</p>
2. TEAEs	Based on reported MedDRA PTs	<p><b>TEAEs occurring within 72 hours after rIX-FP administration:</b>  All 3 events with PT of Hypersensitivity.</p> <p><b>Related TEAEs:</b>  All 3 events with PT of Hypersensitivity and only 1 event with PT of Rash.</p> <p><b>TEAEs occurring in more than 1 subject:</b>  Only PTs of Rash (4 events) and Urticaria (2 events).</p>

Thus, the apparent divergence noted by the assessor is due to the different selection criteria for these different analyses. While the data / analyses are consistent and correct, CSLB made some minor adjustments for clarity in Section 2.5.5.2.2.2 of the Clinical Overview.

### Assessment of the MAH's response

Three individuals experienced symptoms of hypersensitivity. From the header of the table it is not clear, if the last column ("within 72 h of rIX-FP") reflects start or resolve of the symptoms.

One patient suffered from two events of exanthema. This was rated as non-serious/non-related.

A second patient suffered from whole-body-urticaria, and skin rash of both lower legs and both forearms, and of skin rash of the face and belly. No timely relationship has been presented. The first skin-rash was rated as "related", the other events as non-related. It is not overt, if these latter events were at the same time. The rashes might be interpreted as "generalized". The third patient is the "inhibitor-patient" of 11 years of age, who overall presented with an exceptional history. He experienced a hypersensitivity reaction, urticaria, and two allergic reactions, most of them rated as related. All of them resulted in drug interruption, and finally withdrawal.

Overall, the description suggests some degree of hypersensitivity potential – not unusual in the respective population. Of note, the presented differentiated presentation of TEAEs and AESIs is not questioned. The amended explanations enlighten the relevant clinical context.

### Conclusion: Point is solved.

## Question 12

At least one subject experienced an SAE of "Device Related Infection". All device related complications (including non-serious) should be presented, irrespective of causal relation.

### Summary of the MAH's response

There were no TEAEs reported for Mix2Vial™, the Idelvion-specific water transfer device, ie, no device-related complications occurred.

There were 2 cases of catheter-related complications per preferred and reported terms ([Table 9](#)) in the context of use of a central venous catheter in young children, as part of standard clinical care: 1 SAE with reported term "hospital admission for infected portacath" which is described in the SAE section of the Clinical Overview, and 1 nonserious event with preferred term Catheter site bruise that occurred in 1 other subject. Both events were not related to investigational product and resolved.

**Table 9 Summary of Catheter-Related Complications (PUP Safety Population, Arm 4)**

<b>Subject ID Age at Screening</b>	<b>System Organ Class / Preferred Term / Reported Term</b>	<b>Duration (Days) / Serious</b>	<b>Severity / Causal Relationship</b>	<b>Action Taken / Outcome</b>
0 year	Infections and infestations/ <b>Device related infection/</b> <i>Hospital admission for infected portacath</i>	12 / Yes Hospitalized	Moderate / <i>Not related</i>	Not applicable / <i>Recovered / resolved</i>
0 year	General disorders and administration site conditions/ <b>Catheter site bruise/</b> <i>Port site bruising</i>	27/ No	Mild / <i>Not related</i>	Not applicable / <i>Recovered / resolved</i>

PUP = previously untreated patient.

Source: CSL654\_3003 PUP CSR [Listing 16.2.7.1.1.1.99](#)

### Assessment of the MAH's response

In addition to the previously described "Device related infection", a serious (hospital admission) portacath infection, one further device related complication has been documented. This latter was a non-serious port-site bruising which lasted 27 days, and resolved.

The number and clinical presentation is in accordance with complications recorded for similar substitution products used in this respective age-group.

### Conclusion: Point is solved

## Clinical Overview:

### **Question 13**

Clinical Overview should be updated according to the assessment for presenting meaningful data. PK-results should be presented as median and range. Key efficacy and safety data should be amended according to the assessment. Presentation of inhibitor development should rely on those (6) subjects with  $\geq 50$  EDs. Further, other significant events including hypersensitivities and device-related complications should be addressed, adequately.

### **Summary of the MAH's response**

CSLB has amended the Clinical Overview to reflect the relevant information from above responses at the appropriate level of detail. A redline version of the Clinical Overview is provided in the working documents folder, the clean updated version in Module 2.5.

CSLB does not address device-related complications in the Clinical Overview, as there were no TEAEs associated with the Mix2Vial™ water transfer device, and the 2 cases of catheter-

### **Assessment of the MAH's response**

Clinical Overview has been amended according to the additional requests.

### **Conclusion: Point is solved**

## SmPC:

### **Question 14**

Substantial abbreviation of the proposed SmPC-amendments is requested, according to the assessment and to the comments made in the attached product information (please, refer to Attachment 1).

### **Summary of the MAH's response**

CSLB agrees with the updates recommended by the rapporteur in section 4.2 of the SmPC and has made respective amendments in the SmPC.

CSLB also agrees with the principle that only substantial results for the PUP population should be reflected in the SmPC.

However, CSLB does not agree with the rapporteur's conclusion that the PUP arm of Study CSL654\_3003 was stopped prematurely and for that reason would not contribute substantial results. The number of enrolled PUPs and study design were endorsed by PDCO "Opinion of PDCO on the acceptance of a modification of an agreed Paediatric Investigation Plan" (EMA-001107-PIP01-10-M04). CSLB performed the PUP study in accordance with the amended study protocol. In the PUP arm of CSL654\_3003, 8 PUPs achieved  $\geq 50$  EDs during on-demand, prophylaxis, surgical, and PK periods (see also CSLB's responses to Questions 7 and 8). For this reason, CSLB has not implemented the changes proposed by the rapporteur under Description of selected adverse reactions in section 4.8. The revised proposals for section 5.1 (including the number of PUPs with at least 50 EDs, originally proposed by the rapporteur for section 4.8) take into consideration the updates made at the request of the rapporteur in Module 2.5 Clinical Overview to ensure the SmPC provides meaningful information about PUPs that will be helpful for health professionals.

For details, please refer to PIQ form and redlined SmPC text.

### **Assessment of the MAH's response**

Proposed amendment of the SmPC is considered to be acceptable, in part.

However, the wording in section 5.1 should still be reduced to the most relevant information in such narrow patient collective. More detailed information on the study is available through the EPAR and EU Clinical Trials Register.

**Conclusion: Point not solved**

### ***RMP aspects***

#### **Question 15**

The MAH should update the summary of safety concerns to:

##### Important identified risks

- Hypersensitivity / anaphylactic reactions
- Development of inhibitors to factor IX

##### Important potential risks

- TEEs

##### Missing information

- Experience in pregnancy and lactation, including labour and delivery
- Experience in elderly patients

### **Summary of the MAH's response**

The MAH acknowledges the assessor's comments that "experience in pregnancy and lactation including labour and delivery" and "experience in geriatric patients (65 years and older)" should continue to be considered missing information and would herewith like to present an extended rationale for removing these as "missing information" for the purpose of the Risk Management Plan (RMP), despite there being limited information available in these patient groups. This is based on the general considerations regarding pharmacovigilance activities and RMP guidance and the specific arguments provided in the subsections below.

The MAH would like to also clarify that removing these items as "missing information" for the purposes of RMP will not change our routine or additional pharmacovigilance activity, which will continue to include the Follow-Up-Questionnaire (FU-Q) for Experience in Pregnancy & Pregnancy Outcomes and our participation in the Haemophilia Network Registry: European Haemophilia Safety Surveillance (EUHASS) to obtain long-term safety data including experience in elderly patients. These topics are routinely included in the PSURs as well.

Following completion of the PUP study, the MAH has taken the opportunity to fully align with the concepts within "GVP Module V - Risk management systems (Rev 2)" and "Guidance on the format of the Risk Management Plan (RMP) in the EU – in integrated format" in updating the content of the EU-RMP. In particular, section V.B.1 – Principles of Risk Management of GVP module V, advises that "The RMP is a dynamic document that should be updated throughout the life cycle of the product(s)" and "Given the overall aim of obtaining more information regarding the risk-benefit balance in certain populations excluded in the preauthorization phase, it is expected that as the product matures, the classification as missing information might not be appropriate anymore once new data become available, or when there is no reasonable expectation that the existing or future feasible pharmacovigilance activities could further characterize the safety profile of the product with respect to the areas of missing information."

In addition, “missing information” is described as follows: “missing information for the purpose of the risk management planning refers to gaps in knowledge about the safety of a medicinal product for certain anticipated utilization or for use in particular patient populations, for which there is insufficient knowledge to determine whether the safety profile differs from that characterized so far. The absence of data itself (e.g., exclusion of a population from clinical studies) does not automatically constitute a safety concern. Instead, the risk management planning should focus on situations that might differ from the known safety profile.”

### **Experience in pregnancy and lactation including labour and delivery**

Given the guidance above, a major consideration was whether any reasonable expectation exists in furthering characterization of the safety profile of Idelvion in these patient populations.

Hemophilia B is an X-chromosome linked recessive disorder; therefore, it is more substantially common in men (87%) than in women (5%), with the other 8% where information on gender is not known [WFH Global Survey, 2020]. The target population for Idelvion (rIX-FP) is predominantly male and this is further corroborated by a recent retrospective international chart review describing the real-world use of rIX-FP [Hermans et al, 2020]. Although female patients were not included in the clinical studies for rIX-FP, the MAH acknowledges the assessor’s comment that the safety profile in the female population is not known though being very unlikely to be different from that of males.

The predominant use of rIX-FP in the male patient population is further validated by the postmarketing safety data collected so far, with over 809,474,653 IU sold worldwide, corresponding to 289,098 standard doses, with an estimated exposure of 5560 patient years. The MAH has received only 5 reports concerning the use of rIX-FP in women. This includes 1 literature report describing a 31-year-old female hemophilia B carrier, who received a bolus injection of 6000 IU rIX-FP before vaginal delivery under epidural analgesia without any problems for herself and her child. No cases pertaining to lactation exposure with rIX-FP have been received from postmarketing reporting to date.

Given the limitations of gathering data on pregnancy in patients with hemophilia B, the MAH also reviewed the postmarketing safety data for the MAH’s plasma-derived FIX products (pdFIX). Cumulatively until 31 March 2022, the MAH received only 3 reports concerning the use of pdFIX in females. All 3 cases were nonserious and reported 1 event each (Wrong product administered, Drug ineffective for unapproved indication, No adverse event). The event of No adverse event was reported in a pregnant female, who received pdFIX (INN). The potential for gathering sufficient pregnancy data to characterize the safety profile in this special female population is therefore very unlikely, given the target population for the product, based on its use in the real world against a backdrop of already small female patient pool with a significant proportion of females that are not of childbearing age, and in any given period, of those that are of childbearing age only a small fraction may consider pregnancy. A further consideration was whether the absence of data in this patient group represents an actual safety concern. To date the MAH has no evidence that the safety profile for rIX-FP in pregnant or breastfeeding women will be any different to the known safety profile of the product. Since the active components of rIX-FP are recombinant counterparts of naturally occurring human plasma proteins, it is expected that rIX-FP will be catabolized in the same manner as endogenous FIX. Therefore, these physiological constituents of the human blood are not expected to induce adverse effects on reproduction or the fetus and effects on embryo toxicity and fertility are not expected. The MAH therefore considers it appropriate to remove “experience in pregnancy and lactation including labour and delivery” as missing information, as the revised GVP guidance states that the absence of data itself (eg, exclusion of a population from clinical studies) does not automatically constitute a safety concern. Also,

- The potential for gathering sufficient pregnancy data to characterize the safety profile in this special population is unlikely, because the target population for rIX-FP is predominantly male, as validated from the postmarketing and literature evidence.
- To date, the MAH has no evidence that the safety profile for rIX-FP in pregnant or breastfeeding women will be any different to the known safety profile of the product.
- Routine pharmacovigilance activities would ensure all reports of special situations, ie, use during pregnancy and lactation, are followed up thoroughly with targeted FU-Qs and routinely discussed in PSURs as applicable; and
- There are no additional pharmacovigilance activities to further characterize the use of rIX-FP in female patients.

### **Experience in geriatric patients (65 years and older)**

The MAH agrees with the assessor's comment that the safety in geriatric patients is not yet characterized adequately, though it is very unlikely to be different from the currently known safety profile. Similar to what is described above for "Pregnancy and lactation including labour and delivery", the major considerations for removal of this topic as "missing information" for RMP purposes was whether there is a reasonable expectation to further characterize the safety profile in the geriatric patient population and whether the absence of data in this patient group constitutes a safety concern. The clinical trial program for rIX-FP has not included elderly patients (> 65 years of age) and from the data obtained in the worldwide literature to date, there is a paucity of information regarding use of recombinant FIX products in individuals over 65 years of age. Considering that the active components of rIX-FP are recombinant counterparts of naturally occurring human plasma proteins, it can be hypothesized that similar pharmacological effects could be expected in this patient population as compared to younger patients. To date the MAH has no evidence that the safety profile for rIX-FP in the geriatric population will be any different to the known safety profile of the product. Cumulatively, 14 cases were reported for rIX-FP in the postmarketing experience in patients aged older than 65 years of age. Although the cases lacked sufficient information for further assessment, these cases did not identify any safety relevant information specific to this age group and this topic will continue to be routinely discussed in the PSURs. This topic is also subject to the MAH's routine signal detection activities for all products, and therefore reviewed on an ongoing basis. Any findings from routine review will follow the MAH's signal detection and evaluation procedures, and any signals will be reported in PSURs. The MAH therefore considers it appropriate to remove "experience in geriatric patients (65 years and older)" as missing information, as the revised GVP guidance states that the absence of data itself (eg, exclusion of a population from clinical studies) does not automatically constitute a safety concern. Also,

- The active components of rIX-FP are recombinant counterparts of naturally occurring human plasma proteins, and similar pharmacological effects could be expected in geriatric patients.
- To date the MAH has no evidence that the safety profile for rIX-FP in the geriatric population will be any different to the known safety profile of the product.
- Routine pharmacovigilance activities including ongoing signal detection analysis will ensure that all reports involving use in special patient populations are followed up thoroughly.
- The MAH's participation in the Hemophilia Network Registry: European Haemophilia Safety Surveillance (EUHASS) will continue to further collect any information on the use of rIX-FP in the geriatric population.

### **References**

[WFH] World Federation of Hemophilia. Report on the Annual Global Survey 2020. Montreal, Canada: October 2021.



Hermans C, Marino R, Lambert C, Mangles S, Sommerer P, Rives V, Maro G, Malcangi G. Real-World Utilisation and Bleed Rates in Patients with Haemophilia B Who Switched to Recombinant Factor IX Fusion Protein (rIX-FP): A Retrospective International Analysis. *Adv Ther.* 2020 Jun;37(6):2988-2998.

Note: While awaiting assessment of the above response, an updated RMP has not been provided with this submission.

### **Assessment of the MAH's response**

The MAH provided additional rationale for removal of the safety concerns "experience in pregnancy and lactation including labour and delivery" and "experience in geriatric patients (65 years and older)" from missing information. Overall, it is not supported that the risks can be removed from the safety concerns considering there is still lack of evidence on those risks and another safety profile cannot be excluded. In addition, as the cases that were reported provided limited information, no safety issues could be identified and therefore new information should be gathered.

Furthermore, it was discussed that if these safety concerns are to be removed, the routine or additional pharmacovigilance activities would not change, considering the FU-Q for Experience in Pregnancy & Pregnancy Outcomes and participation in the (EUHASS) registry to obtain long-term safety data including experience in elderly patients would continue. However, following GVP V, both pharmacovigilance activities and risk minimisation measures should be related to specific safety concerns. Therefore, since experience in pregnancy and elderly should remain in the safety concerns, these aspects should also remain throughout the RMP. An update of the RMP with inclusion of these risks is requested.

### **Conclusion**

**Issue not resolved.**

### **Question 16**

The MAH should include "patients with severe renal and hepatic impairment", "medication errors" and "Experience in patients for ITI (off-label use)" for monitoring in the PSUR for further evaluation.

### **Summary of the MAH's response**

The MAH would like to confirm that "patients with severe renal and hepatic impairment", "medication errors", and "experience in patients for ITI (off-label use)" will be monitored in the PSUR for further evaluation.

### **Assessment of the MAH's response**

The MAH will monitor "patients with severe renal and hepatic impairment", "medication errors" and "experience in patients for ITI (off-label use)" in the PSUR as requested.

### **Conclusion**

**Issue resolved.**



**Question 17**

The FU-Q for missing information of Experience in pregnancy and pregnancy outcomes should remain as routine pharmacovigilance activity.

**Summary of the MAH's response**

As noted in response to Question 15, the MAH would like to confirm that removing these items as "missing information" for the purposes of RMP will not change our routine pharmacovigilance activity, which will continue to include the FU-Q for Experience in pregnancy. The pregnancy reporting form is routinely used in the MAH to obtain information on all spontaneously reported pregnancies and pregnancy outcomes for all the MAH products, regardless of whether experience during "pregnancy and lactation including labour and delivery" is considered a safety concern or not.

**Assessment of the MAH's response**

The MAH has discussed that the FU-Q for "Experience in pregnancy and pregnancy outcomes" will remain in the RMP. This is not accepted as pharmacovigilance activities such as FU-Qs should be related to a specific safety concern. Following assessment of the response in question 15, it is not accepted to remove experience in pregnancy and lactation, including labour and delivery from the safety concerns. Therefore, the FU-Q should remain routine pharmacovigilance activity throughout the RMP. An update of the RMP is requested. Experience in pregnancy and lactation should also be discussed in the PSURs.

**Conclusion**

**Issue not resolved.**

**Question 18**

The elderly population (>65 years) should remain part of participation in EUHASS to collect long-term safety data (additional pharmacovigilance activity).

**Summary of the MAH's response**

As noted in response to Question 15, the MAH would like to also clarify that removing these items as "missing information" for the purposes of RMP will not change our routine or additional pharmacovigilance activity. The MAH will continue our participation in the Haemophilia Network Registry: European Haemophilia Safety Surveillance (EUHASS) to obtain long-term safety data including experience in elderly patients. These topics will be routinely included in the PSURs as applicable.

**Assessment of the MAH's response**

The MAH has clarified that the elderly population will remain to be analysed in the EUHASS registry and discussed in the PSURs. Considering the elderly population (>65 years) was not accepted to remove as missing information from the safety concerns, the RMP should include information of the elderly population in EUHASS. An update is requested.

**Conclusion**

**Issue not resolved.**

RMP version 4.0 with DLP 26 January 2022 and date of final sign off 01 April 2022 is not acceptable.

☒ Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

## **13. 2<sup>nd</sup> request for supplementary information**

### **13.1. Major objections**

None

### **13.2. Other concerns**

#### ***Clinical aspects***

SmPC:

1. (From Q 14) Abbreviation of the proposed SmPC-amendments is still requested, considering the narrow data-base (please, refer to Attachment).

#### ***RMP aspects***

2. "Experience in pregnancy and lactation including labour and delivery" and "experience in geriatric patients (65 years and older)" should remain in the safety concerns. These aspects should remain throughout the RMP. An update of the RMP with inclusion of these risks is requested.
3. FU-Q for ""Experience in pregnancy and pregnancy outcomes" should remain routine pharmacovigilance activity throughout the RMP. An update of the RMP is requested. Experience in pregnancy and lactation should also be discussed in the PSURs.
4. Considering the elderly population (>65 years) was not accepted to be removed as missing information from the safety concerns, the RMP should include information of the elderly population in EUHASS. An update is requested.

## 14. Assessment of the responses to the 2<sup>nd</sup> request for supplementary information

### *Clinical aspects*

#### **Question 1**

(From Q 14) Abbreviation of the proposed SmPC-amendments is still requested, considering the narrow data-base (please, refer to Attachment).

#### **Summary of the MAH's response**

CSLB agrees with abbreviations proposed by Rapporteur for SmPC.

CSLB proposes to indicate in section 4.8 Undesirable effects that in PUP study was reported one case with high-titre inhibitor, that would provide more accurate information and help to evade misinterpretation.

Also, CSLB proposes to add in section 5.1, subsection Clinical efficacy information on annualized spontaneous bleeding rate (AsBR) and believes that this information is relevant for physicians and provides important information especially for paediatric population, because AsBR doesn't depend on lifestyle and isn't related to traumatic or surgical bleedings.

#### **Assessment of the MAH's response**

The MAH proposes to reflect the number of "one" inhibitor in the population of the PUP study (section 4.8). It was, however, intended to avoid the misleading "incidence" of 1 in 8 PUPs (12.5%) with >50 EDs. This is overtly much higher than the rare inhibitor incidence in Hemophilia B (1.5-3%). Further, the reported case was extraordinary, and might therefore unintentionally increase such "incidence". However, the MAHs proposal is taken.

Regarding reflection of "spontaneous" ABR: The theoretical idea as presented by the MAH ("AsBR does not depend on lifestyle") is hampered by real infant's life: It will be difficult to clearly discriminate e.g. between a non-recognized bagatelle-trauma – documented as a spontaneous bleed and a small trauma – documented as a non-spontaneous bleed, especially in lively healthy infants under normal and not specific "neutral" observation. Therefore, the discrimination between ABR and AsBR is considered to be artificial, and potentially manipulable. Further, no standardized applicable and comparable definition is available (please, also refer to the discussions in this Assessment Report). Thus, AsBR should not be reflected in section 5.1.

**Of note**, due to inadvertent circumstances, changes in Section 5.1 of the SmPC-version from 20<sup>th</sup> Oct 2022 have not been included, completely. These should also be taken. Please, refer to the attached document.

#### **Conclusion**

The MAHs proposal regarding section 4.8 is taken.

The MAH is asked to amend section 5.1 as proposed in the attached SmPC document.

☒ Overall conclusion and impact on benefit-risk balance has/have been updated accordingly.

## ***RMP aspects***

### **Question 2**

"Experience in pregnancy and lactation including labour and delivery" and "experience in geriatric patients (65 years and older)" should remain in the safety concerns. These aspects should remain throughout the RMP. An update of the RMP with inclusion of these risks is requested.

### **Summary of the MAH's response**

CSLB acknowledges the assessor's comments and has retained "Experience in pregnancy and lactation including labour and delivery" and "experience in geriatric patients (65 years and older)" in the safety concerns section of the RMP. The updated RMP with this information has been submitted.

### **Assessment of the MAH's response**

The MAH submitted RMP version 4.1 with DLP 26 January 2022 and date of final sign off 07 December 2022. Both "Experience in pregnancy and lactation including labour and delivery" and "experience in geriatric patients (65 years and older)" were included as missing information in the safety concerns. All other relevant sections were updated.

### **Conclusion**

Issue resolved.

### **Question 3**

FU-Q for "Experience in pregnancy and pregnancy outcomes" should remain routine pharmacovigilance activity throughout the RMP. An update of the RMP is requested. Experience in pregnancy and lactation should also be discussed in the PSURs.

### **Summary of the MAH's response**

CSLB acknowledges the assessor's comments. There is no change to the FU-Q on "Experience in pregnancy and pregnancy outcomes" as a routine pharmacovigilance activity and this topic will be discussed in the PSURs.

### **Assessment of the MAH's response**

The FU-Q for "Experience in pregnancy and lactation including labour and pregnancy outcomes" was included as requested. Annex 4 was updated with a pregnancy reporting form and pregnancy reporting outcome form. Accepted.

### **Conclusion**

Issue resolved.

**Question 4**

Considering the elderly population (>65 years) was not accepted to be removed as missing information from the safety concerns, the RMP should include information of the elderly population in EUHASS. An update is requested.

**Summary of the MAH's response**

CSLB acknowledges the assessor's comments. The RMP has been updated to retain the information on the elderly population in EUHASS.

**Assessment of the MAH's response**

The elderly population remains included in EUHASS for evaluation as requested. Accepted.

**Conclusion**

Issue resolved. RMP version 4.1 can be considered acceptable.

☒ Overall conclusion and impact on benefit-risk balance has/have been updated accordingly.

## 15. 3<sup>rd</sup> request for supplementary information

1. SmPC-amendment to section 5.1 is still requested and a revised product information should be submitted accordingly (please, refer to Attachment 1).

## 16. Assessment of the responses to the 3<sup>rd</sup> request for supplementary information

### Question 1

SmPC-amendment to section 5.1 is still requested and a revised product information should be submitted accordingly (please, refer to Attachment 1).

### Summary of the MAH's response

CSL Behring agrees with the assessor's comments and has amended Section 5.1 of the SmPC accordingly. Minor clarification was added in section 5.1 to ensure correct understanding.

### Assessment of the MAH's response

Proposed changes to the Product information have been taken. Last paragraph of Section 5.1 has been amended for correct understanding. The product information (eCTD 0128) is considered acceptable.

### Conclusion: Point is solved.

☒ Overall conclusion and impact on benefit-risk balance has/have been updated accordingly.

## Reminders to the MAH

1. The MAH is reminded to submit an eCTD closing sequence with the final documents provided by Eu-dralink during the procedure (including final PI translations, if applicable) within 15 days after the Commission Decision, if there will be one within 2 months from adoption of the CHMP Opinion, or prior to the next regulatory activity, whichever is first. If the Commission Decision will be adopted within 12 months from CHMP Opinion, the closing sequence should be submitted within 30 days after the Opinion or 5 days after the submission by the MAH of the final language translations, when there is a linguistic review. For additional guidance see chapter 4.1 of the [Harmonised Technical Guidance for eCTD Submissions in the EU](#)